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STRUCTURE FILE UPDATES: 19 JUN 2002 HIGHEST RN 432491-02-6  
DICTIONARY FILE UPDATES: 19 JUN 2002 HIGHEST RN 432491-02-6

TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

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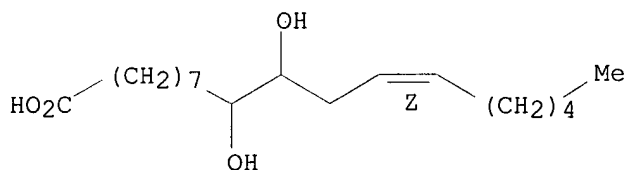
Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES  
for more information. See STNote 27, Searching Properties in the CAS  
Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> d ide can tot 170

L70 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2002 ACS  
RN 263399-34-4 REGISTRY  
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (12Z)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C18 H34 O4  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER

Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

4 REFERENCES IN FILE CA (1967 TO DATE)  
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:163965

REFERENCE 2: 134:143071

REFERENCE 3: 133:360357

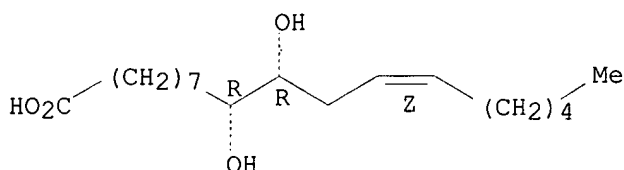
REFERENCE 4: 132:262485

L70 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS  
RN 189191-41-1 REGISTRY  
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)  
OTHER CA INDEX NAMES:  
CN 12-Octadecenoic acid, 9,10-dihydroxy-, [R\*,R\*-(Z)]-  
OTHER NAMES:  
CN Leukotoxin diol

Jan Delaval  
Reference Librarian  
Biotechnology & Chemical Library  
CM1 1E07 - 703-308-4498  
[jan.delaval@uspto.gov](mailto:jan.delaval@uspto.gov)

FS STEREOSEARCH  
 DR 59959-42-1  
 MF C18 H34 O4  
 SR CA  
 LC STN Files: BEILSTEIN\*, BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL  
 (\*File contains numerically searchable property data)

Relative stereochemistry.  
 Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

9 REFERENCES IN FILE CA (1967 TO DATE)  
 9 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:116492  
 REFERENCE 2: 133:70547  
 REFERENCE 3: 132:318802  
 REFERENCE 4: 132:318745  
 REFERENCE 5: 131:168305  
 REFERENCE 6: 129:36394  
 REFERENCE 7: 128:201056  
 REFERENCE 8: 127:230447  
 REFERENCE 9: 126:289133

L70 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS

RN 60-33-3 REGISTRY

CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 9,12-Octadecadienoic acid (Z,Z)-

CN Linoleic acid (8CI)

OTHER NAMES:

CN (Z,Z)-9,12-Octadecadienoic acid

CN .alpha.-Linoleic acid

CN 9,12-Octadecadienoic acid, (Z,Z)-

CN 9-cis,12-cis-Linoleic acid

CN 9Z,12Z-Linoleic acid

CN all-cis-9,12-Octadecadienoic acid

CN cis,cis-Linoleic acid

CN cis-.DELTA.9,12-Octadecadienoic acid

CN cis-9,cis-12-Octadecadienoic acid

CN Emersol 315

CN Extra Linoleic 90

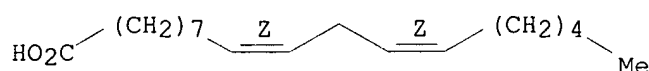
CN Linolic acid

CN Polylin 515

CN Unifac 6550

FS STEREOSEARCH  
 MF C18 H32 O2  
 CI COM  
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM\*, DIOGENES, DIPPR\*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, GMELIN\*, HODOC\*, HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM\*, PIRA, PROMT, RTECS\*, SPECINFO, TOXCENTER, TULSA, USPAT2, USPATFULL, VETU  
 (\*File contains numerically searchable property data)  
 Other Sources: DSL\*\*, EINECS\*\*, TSCA\*\*  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)

Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

24941 REFERENCES IN FILE CA (1967 TO DATE)  
 1106 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 24987 REFERENCES IN FILE CAPLUS (1967 TO DATE)  
 10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 136:395039  
 REFERENCE 2: 136:393328  
 REFERENCE 3: 136:391350  
 REFERENCE 4: 136:391071  
 REFERENCE 5: 136:391045  
 REFERENCE 6: 136:390753  
 REFERENCE 7: 136:390501  
 REFERENCE 8: 136:387668  
 REFERENCE 9: 136:387667  
 REFERENCE 10: 136:387465

=> d his

(FILE 'REGISTRY' ENTERED AT 16:28:38 ON 21 JUN 2002)

DEL HIS

E LINOLEIC ACID/CN

L1 1 S E3

L2 5 S C18H32O2/MF AND 9 12 OCTADECADIENOIC ACID NOT (LABELED OR (D

FILE 'HCAPLUS' ENTERED AT 16:30:25 ON 21 JUN 2002

E LEUKOTOXINDIOL

L3 15 S E1,E4,E5 (L) DIOL

FILE 'REGISTRY' ENTERED AT 16:32:01 ON 21 JUN 2002

L4 1 S 189191-41-1  
 L5 10 S C18H34O4/MF AND 12 OCTADECENOIC ACID AND 9 10 DIHYDROXY NOT  
 L6 10 S L4,L5

FILE 'HCAPLUS' ENTERED AT 16:33:44 ON 21 JUN 2002

L7 33 S L6  
 L8 39 S L3,L7  
 L9 100 S (L1 OR LINOLEIC ACID) (L)DIOL  
 L10 125 S L8,L9  
 L11 8 S L10 AND (?HYPERTENS? OR ARDS OR (ADULT OR ACUTE) (L)RESPIR?(L)  
 E HAMMOCK B/AU  
 L12 510 S E3-E8  
 E ZUREK G/AU  
 L13 8 S E3,E4  
 E GEE S/AU  
 L14 148 S E3-E10,E21,E22  
 E NEWMAN J/AU  
 L15 81 S E3,E29  
 E NEWMAN JOHN/AU  
 L16 318 S E3,E36,E37  
 L17 12 S L10 AND L12-L16  
 E CARDIOVASCULAR/CT  
 E E6+ALL  
 L18 67 S E1  
 E E2+ALL  
 L19 5360 S E4  
 L20 281115 S E3+NT  
 E HYPERTENSION/CT  
 E E3+ALL  
 L21 33653 S E2+NT  
 E E8+ALL  
 L22 23168 S E3+NT  
 L23 40210 S E8+NT  
 L24 118127 S E7+NT  
 E ADULT RESPIRATORY DISTRESS SYNDROME/CT  
 E E3+ALL  
 L25 31 S E1  
 L26 1395 S E2  
 E PREECLAMPSIA/CT  
 E E3+ALL  
 L27 2169 S E3,E4,E2+NT  
 L28 3737 S E3-E9/BI  
 E LIPID METABOLISM/CT  
 E E3 ALL  
 E LIPID METABOLISM/CT  
 E E3+ALL  
 L29 11021 S E1,E2  
 L30 6 S L10 AND L18-L29  
 L31 14 S L11,L17,L30  
 E FATTY ACIDS/CT  
 E FATTY ACIDS(L)D/CT  
 E UNSATURATED FATTY ACIDS/CT  
 E E3+ALL  
 L32 8133 S E1,E2  
 L33 48 S L32 (L) (DIHYDROXY# OR DIOH OR DIOL OR DI HYDROXY# OR DI OH)  
 L34 13 S L33 NOT (PLASTIC# OR COATING?)/SC,SX  
 L35 3 S L34 AND (1 OR 9 OR 63)/SC,SX  
 L36 320 S L32 AND L18-L29  
 L37 5 S L36 AND 9/SC  
 SEL DN 2  
 L38 1 S L37 AND E1  
 L39 422 S L32 (L) (ANT OR ANST)/RL  
 L40 6 S L39 AND L36

```
SEL DN 3
L41      1 S L40 AND E2
L42     15 S L31,L38,L41
L43      1 S L10 (L) (ANT OR ANST)/RL
L44      0 S L10 AND (BLOOD ANALYSIS OR URINALYSIS)
L45      8 S L10 AND ?ASSAY?
SEL DN 1 2 5
L46      3 S L45 AND E3-E5
L47     16 S L42,L46
L48      0 S L10 AND ELISA
L49      7 S L10 AND (BLOOD OR URINE)
E BLOOD/CT
E E3+ALL
L50      4 S L10 AND E2+NT
L51      0 S L10 AND (E136+NT OR E139+NT OR E145+NT)
E URINE/CT
E E3+ALL
L52      0 S L10 AND E3+NT
L53      1 S L10 AND E2+NT
L54      5 S L10 AND E1+NT
E URINE ANALYSIS/CT
E E3+ALL
L55      0 S L10 AND E3,E2+NT
L56     24 S L47,L49,L50,L53,L54
L57      9 S L56 AND L1,L2
L58     16 S L56 AND ?LINOLE?
L59     17 S L57,L58
L60      7 S L56 NOT L59
L61      6 S L60 NOT WASP
L62     23 S L59,L61
SEL DN 6 18 19 20 21 22 23
L63     16 S L62 NOT E1-E7
L64     16 S L63 AND L3,L7-L63
L65     14 S L64 AND LEUKOTOX?
L66     16 S L64,L65
L67      7 S LINOLE? (L) ?GLUCURON? (L) ?CONJUGAT?
SEL DN 1
L68      1 S L67 AND E8
L69     16 S L66,L68
SEL HIT RN
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FILE 'REGISTRY' ENTERED AT 17:05:40 ON 21 JUN 2002  
L70 3 S E9-E11

FILE 'REGISTRY' ENTERED AT 17:05:59 ON 21 JUN 2002

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 17:06:08 ON 21 JUN 2002  
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FILE COVERS 1907 - 21 Jun 2002 VOL 136 ISS 25  
FILE LAST UPDATED: 19 Jun 2002 (20020619/ED)

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=> d all hitstr tot 169

L69 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 2002 ACS  
AN 2001:863088 HCAPLUS  
DN 136:116492  
TI **Leukotoxin-Diol. A putative toxic mediator involved in acute respiratory distress syndrome**  
AU Zheng, Jiang; Plopper, Charles G.; Lakritz, Jeffery; Storms, David H.; Hammock, Bruce D.  
CS Department of Pharmaceutical Sciences, School of Pharmacy, Bouve College of Health Sciences, Northeastern University, Boston, MA, 02115, USA  
SO American Journal of Respiratory Cell and Molecular Biology (2001), 25(4), 434-438  
CODEN: AJRBEL; ISSN: 1044-1549  
PB American Thoracic Society  
DT Journal  
LA English  
CC 14-4 (Mammalian Pathological Biochemistry)  
AB **Leukotoxin** is clin. assocd. with **acute respiratory distress syndrome (ARDS)** ). Recently, we found that **leukotoxin-diol**, the hydrated product of **leukotoxin**, is more toxic than the parent **leukotoxin** in vitro. To test if this difference in the toxicity of **leukotoxin** and **leukotoxin-diol** exists in vivo, Swiss Webster mice were administered **leukotoxin** or **leukotoxin-diol**. All mice treated with **leukotoxin-diol** died of **ARDS-like respiratory distress**, whereas the animals exposed to **leukotoxin** at the same dose survived. Histopathol. evaluation of the lungs revealed massive alveolar edema and hemorrhage with interstitial edema around **blood** vessels in the lungs of mice treated with **leukotoxin-diol**, whereas the lungs of mice treated with identical doses of **leukotoxin** had perivascular edema only and little change in alveolar spaces. Immunohistochem. showed that the sol. epoxide hydrolase responsible for the hydrolysis of **leukotoxin** to its **diol** is concd. in the vascular smooth muscle of small and medium-sized pulmonary vessels. In addn., 4-phenylchalcone oxide, an inhibitor of sol. epoxide hydrolase, was found to decrease the mortality induced by **leukotoxin** but had no effect on mortality induced by **leukotoxin-diol**. These studies provide strong in vivo evidence that **leukotoxin** may act as a protoxicant and that the corresponding **diol** is a putative toxic mediator involved in the development of **ARDS**.  
ST **leukotoxin diol** toxic mediator respiration distress syndrome  
IT **Respiratory distress syndrome**  
(acute; **leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)  
IT Lung  
(alveolus; **leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory**

distress syndrome in mice)

IT Hydrolysis  
(biol.; leukotoxin-diol. a putative toxic mediator involved in acute respiratory distress syndrome in mice)

IT Lung, disease  
(injury; leukotoxin-diol. a putative toxic mediator involved in acute respiratory distress syndrome in mice)

IT Edema  
Hemorrhage  
(leukotoxin-diol. a putative toxic mediator involved in acute respiratory distress syndrome in mice)

IT Toxins  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(leukotoxins; leukotoxin-diol. a putative toxic mediator involved in acute respiratory distress syndrome in mice)

IT Blood vessel  
(smooth muscle; leukotoxin-diol. a putative toxic mediator involved in acute respiratory distress syndrome in mice)

IT 189191-41-1, Leukotoxin-Diol  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(leukotoxin-diol. a putative toxic mediator involved in acute respiratory distress syndrome in mice)

IT 2403-28-3D, 4-Phenylchalcone, oxide 9048-63-9, Epoxide hydrolase  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(leukotoxin-diol. a putative toxic mediator involved in acute respiratory distress syndrome in mice)

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

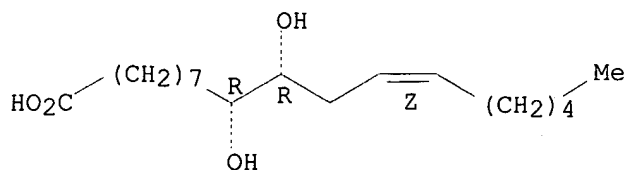
- (1) Demling, R; Annu Rev Med 1995, V46, P193 HCAPLUS
- (2) Grant, D; Biochem Pharmacol 1996, V51, P503 HCAPLUS
- (3) Hayakawa, M; Biochem Biophys Res Commun 1989, V161, P1077 HCAPLUS
- (4) Hsu, S; J Histochem Cytochem 1981, V10, P1079
- (5) Hu, J; Lung 1988, V166, P327 HCAPLUS
- (6) Kosaka, K; Mol Cell Biochem 1994, V139, P141 HCAPLUS
- (7) Lee, M; Science 1998, V280, P915 MEDLINE
- (8) Moghaddam, M; Nature Med 1997, V3, P562 HCAPLUS
- (9) Moran, J; Toxicol Appl Pharmacol 1997, V146, P53 HCAPLUS
- (10) Mullin, C; Arch Biochem Biophys 1982, V216, P423 HCAPLUS
- (11) Ozawa, T; Am Rev Respir Dis 1988, V137, P535 HCAPLUS
- (12) Ozawa, T; Biochem Biophys Res Commun 1988, V152, P1310 HCAPLUS
- (13) Plopper, C; Exp Lung Res 1987, V13, P59 HCAPLUS
- (14) Street, J; J Biol Chem 1996, V271, P3507 HCAPLUS
- (15) Vaitukaitis, J; Methods Enzymol 1981, V73, P46 MEDLINE
- (16) Wixtrom, R; Anal Biochem 1988, V169, P71 HCAPLUS

IT 189191-41-1, Leukotoxin-Diol  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(leukotoxin-diol. a putative toxic mediator involved in acute respiratory distress syndrome in mice)

RN 189191-41-1 HCAPLUS

CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.  
Double bond geometry as shown.



L69 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 2001:539978 HCAPLUS

DN 135:148461

TI Cellular Characterization of **Leukotoxin Diol**-Induced Mitochondrial Dysfunction

AU Sisemore, Marlene F.; Zheng, Jiang; Yang, Joy C.; Thompson, David A.; Plopper, Charles G.; Cortopassi, Gino A.; Hammock, Bruce D.

CS Department of Entomology, University of California, Davis, CA, 95616, USA

SO Archives of Biochemistry and Biophysics (2001), 392(1), 32-37

CODEN: ABBIA4; ISSN: 0003-9861

PB Academic Press

DT Journal

LA English

CC 4-5 (Toxicology)

Section cross-reference(s): 1, 14

AB **Leukotoxin**, a cytochrome P 450-derived epoxide of **linoleic acid**, has been implicated as a causative factor in **acute respiratory distress**

**syndrome**. Conversion of this fatty acid epoxide to **leukotoxin diol** by epoxide hydrolase has been hypothesized as the crit. activation step in **leukotoxin**-induced cellular toxicity. In both human and insect cells, we obsd. that **leukotoxin diol** causes **acute** cellular toxicity and that cyclosporin A, an inhibitor of the mitochondrial permeability transition, ameliorates **leukotoxin diol**-assocd. toxicity. To evaluate mitochondria as a target of **leukotoxin diol**, multiple aspects of mitochondrial integrity were evaluated in both cell- and organelle-based **assays**. **Leukotoxin diol** specifically activated the mitochondrial permeability transition, resulting in release of cytochrome c and subsequent cell death. Pretreatment with cyclosporin A inhibited these effects and, furthermore, limited in vivo toxicity. While the mechanisms underlying **leukotoxin**-mediated toxicity remain to be fully elucidated, the observation that **leukotoxin diol** disrupts mitochondrial function specifically through activation of the mitochondrial permeability transition suggests at least one mechanism through which **leukotoxin diol** may exert its activity in physiol. contexts. (c) 2001 Academic Press.

ST **leukotoxin diol** mitochondria cell death

IT Animal cell line

(SF21, insect; cellular characterization of **leukotoxin diol**-induced mitochondrial dysfunction)

IT Cell death

HeLa cell

Mitochondria

Respiratory distress syndrome

(cellular characterization of **leukotoxin diol**-induced mitochondrial dysfunction)

IT Toxins

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (**leukotoxins**; cellular characterization of **leukotoxin diol**-induced mitochondrial dysfunction)

IT 21019-43-2, Methyl **leukotoxin** 189191-42-2, Methyl **leukotoxin diol**



RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(cellular characterization of **leukotoxin diol**  
-induced mitochondrial dysfunction)

IT 59865-13-3, Cyclosporin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(cellular characterization of **leukotoxin diol**  
-induced mitochondrial dysfunction)

IT 9007-43-6, cytochrome c, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(cellular characterization of **leukotoxin diol**  
-induced mitochondrial dysfunction)

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Bossy-Wetzel, E; Embo J 1998, V17, P37 HCAPLUS
- (2) Demling, R; Annu Rev Med 1995, V46, P193 HCAPLUS
- (3) Green, D; Science 1998, V281, P1309 HCAPLUS
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- (23) Yang, J; Science 1997, V275, P1129 HCAPLUS

L69 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 2001:170554 HCAPLUS

DN 135:15220

TI The Role of Methyl-Linoleic Acid Epoxide and  
Diol Metabolites in the Amplified Toxicity of Linoleic  
Acid and Polychlorinated Biphenyls to Vascular Endothelial Cells

AU Slim, Rabih; Hammock, Bruce D.; Toborek, Michal; Robertson,  
Larry W.; Newman, John W.; Morisseau, Christophe H. P.; Watkins,  
Bruce A.; Saraswathi, Viswanathan; Hennig, Bernhard

CS Graduate Center for Toxicology, University of Kentucky, Lexington, KY,  
40506-0054, USA

SO Toxicology and Applied Pharmacology (2001), 171(3), 184-193  
CODEN: TXAPA9; ISSN: 0041-008X

PB Academic Press

DT Journal

LA English

CC 4-3 (Toxicology)

Section cross-reference(s): 18

AB Selected dietary lipids may increase the atherogenic effects of  
environmental chems., such as polychlorinated biphenyls (PCBs), by  
cross-amplifying mechanisms leading to dysfunction of the vascular  
endothelium. The authors have shown previously that the .omega.-6 parent  
fatty acid, **linoleic acid**, or 3,3',4,4'-  
tetrachlorobiphenyl (PCB 77), an aryl hydrocarbon (Ah) receptor agonist,

independently can cause disruption of endothelial barrier function. Furthermore, cellular enrichment with **linoleic acid** can amplify PCB-induced endothelial cell dysfunction. The authors hypothesize that the amplified toxicity of **linoleic acid** and PCBs to endothelial cells could be mediated in part by cytotoxic epoxide metabolites of **linoleic acid** called **leukotoxins** (LTX) or their **diol** derivs. (LTXD). Exposure to LTXD resulted in a dose-dependent increase in albumin transfer across endothelial cell monolayers, whereas this disruption of endothelial barrier function was obsd. only at a high concn. of LTX. Pretreatment with the cytosolic epoxide hydrolase inhibitor 1-cyclohexyl-3-dodecyl urea partially protected against the obsd. LTX-induced endothelial dysfunction. Endothelial cell activation mediated by LTX and/or LTXD also enhanced nuclear translocation of the transcription factor NF- $\kappa$ B and gene expression of the inflammatory cytokine IL-6. Inhibiting cytosolic epoxide hydrolase decreased the LTX-mediated induction of both NF- $\kappa$ B and the IL-6 gene, whereas the antioxidant vitamin E did not block LTX-induced endothelial cell activation. Most importantly, inhibition of cytosolic epoxide hydrolase blocked both **linoleic acid**-induced cytotoxicity, as well as the additive toxicity of **linoleic acid** plus PCB 77 to endothelial cells. Interestingly, cellular uptake and accumulation of **linoleic acid** was markedly enhanced in the presence of PCB 77. These data suggest that cytotoxic epoxide metabolites of **linoleic acid** play a crit. role in **linoleic acid**-induced endothelial cell dysfunction. Furthermore, the severe toxicity of PCBs in the presence of **linoleic acid** may be due in part to the generation of epoxide and **diol** metabolites. These findings have implications in understanding interactive mechanisms of how dietary fats can modulate dysfunction of the vascular endothelium mediated by certain environmental contaminants. (c) 2001 Academic Press.

ST PCB **linoleic acid leukotoxin** toxicity endothelium

IT Transcription factors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(NF- $\kappa$ B (nuclear factor  $\kappa$ B); role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Blood vessel

(endothelium; role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Biological transport

(intracellular; role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Toxins

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (**leukotoxins**; role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Cytotoxicity

(role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Fats and Glyceridic oils, biological studies

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (role of Me-**linoleic acid** epoxide and **diol**

metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

## IT Interleukin 6

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

## IT Biological transport

(uptake; role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT 60-33-3, **Linoleic acid**, biological studies

92-52-4D, Biphenyl, chloro derivs. 21019-43-2 32598-13-3, PCB 77 189191-42-2

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)

(role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

## IT 9048-63-9, Epoxide hydrolase

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

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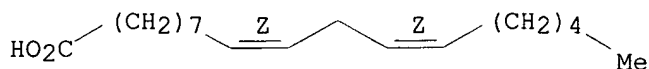
IT 60-33-3, **Linoleic acid**, biological studies

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
 (role of **Me-linoleic acid** epoxide and **diol**  
 metabolites in the amplified toxicity of **linoleic**  
**acid** and polychlorinated biphenyls to vascular endothelial  
 cells)

RN 60-33-3 HCAPLUS

CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L69 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:806272 HCAPLUS

DN 134:173927

TI Toxicity of **linoleic acid** metabolites

AU Greene, Jessica F.; **Hammock, Bruce D.**

CS Departments of Entomology and Environmental Toxicology, University of California at Davis, Davis, CA, 95616, USA

SO Advances in Experimental Medicine and Biology (1999), 469(Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury, 4), 471-477

CODEN: AEMBAP; ISSN: 0065-2598

PB Kluwer Academic/Plenum Publishers

DT Journal; General Review

LA English

CC 4-0 (Toxicology)

AB A review with 22 refs. on the formation of **linoleic acid**

metabolites, synthesis of **leukotoxin** and isoleukotoxin, toxicity of **leukotoxin** and isoleukotoxin, and metabolite toxicity ( **leukotoxin diol** and isoleukotoxin **diol**).

ST review toxicity **linoleic** acid metabolite **leukotoxin** isoleukotoxin

IT Toxins

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(**leukotoxins**; toxicity of **linoleic** acid metabolites)

IT Toxicity

(toxicity of **linoleic** acid metabolites)

IT **60-33-3D, Linoleic** acid, metabolites 126639-26-7, Isoleukotoxin

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(toxicity of **linoleic** acid metabolites)

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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IT **60-33-3D, Linoleic** acid, metabolites

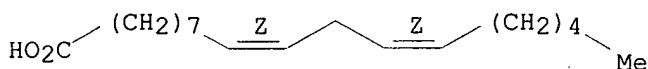
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(toxicity of **linoleic** acid metabolites)

RN 60-33-3 HCAPLUS

CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L69 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:545956 HCAPLUS

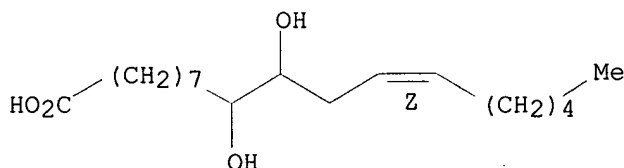
DN 133:360357

TI **Linoleic** Acid Diols Are Novel Substrates for

- Human UDP-Glucuronosyltransferases
- AU Jude, Anthony R.; Little, Joanna M.; Freeman, John P.; Evans, James E.; Radomska-Pandya, Anna; Grant, David F.
- CS Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA
- SO Archives of Biochemistry and Biophysics (2000), 380(2), 294-302  
CODEN: ABBIA4; ISSN: 0003-9861
- PB Academic Press
- DT Journal
- LA English
- CC 7-3 (Enzymes)
- Section cross-reference(s): 13
- AB **Linoleic acid diol glucuronides**  
have been isolated previously from **urine** of patients suffering from generalized peroxisomal disorders. **Glucuronidation** of **linoleic acid** and **linoleic acid diols** by human liver microsomes was studied to investigate the role of **glucuronide conjugation** in the metab. of **linoleic acid diols**. **Glucuronide** products were isolated and analyzed by TLC and HPLC-MS. HPLC-MS showed ions with (m/z) corresponding to singly **glucuronidated linoleic acid diols** while TLC revealed that the **glucuronidation** was at a hydroxyl position. Kinetic anal. gave apparent Km values in the range of 50-200  $\mu$ M and Vmax rates from 5 to 12 nmol/mg  $\cdot$  min. These rates are substantially higher than activities seen for most endogenous hydroxylated substrates. **Assays** using each of the four individually purified **linoleic acid diol** enantiomers suggest that **glucuronidation** occurs at only one of the two hydroxyl groups of each enantiomer. These results show for the first time that hydroxylated fatty acids are actively **glucuronidated** by human liver microsomes and suggest that **glucuronidation** may play a significant role in the biotransformation of **linoleic acid diols** in humans. (c) 2000 Academic Press.
- ST **linoleate** diol hydroxyl group UDP glucuronosyltransferase glucuronylation; enantiomer **linoleate** UDP glucuronosyltransferase substrate kinetics
- IT Enantiomers  
Enzyme kinetics  
Glucuronylation  
Hydroxyl group  
Michaelis constant  
(**linoleic acid diols** are novel substrates for human UDP-glucuronosyltransferases)
- IT 9030-08-4, Uridine diphosphoglucuronosyltransferase  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(**linoleic acid diols** are novel substrates for human UDP-glucuronosyltransferases)
- IT 112-63-0, **Linoleic acid** methyl ester 10547-36-1  
17966-13-1 21019-43-2 61949-82-4 **263399-34-4** 263399-35-5  
306940-00-1 306940-02-3 306940-08-9 306940-10-3 306940-12-5  
306940-14-7 306940-16-9 306940-18-1 306940-20-5 306940-22-7  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(**linoleic acid diols** are novel substrates for human UDP-glucuronosyltransferases)
- RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
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- IT 263399-34-4  
 RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
 (linoleic acid diols are novel substrates for human UDP-glucuronosyltransferases)
- RN 263399-34-4 HCAPLUS  
 CN 12-Octadecenoic acid, 9,10-dihydroxy-, (12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L69 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2002 ACS  
 AN 2000:259098 HCAPLUS  
 DN 133:69968  
 TI Metabolism of Monoepoxides of Methyl Linoleate: Bioactivation and Detoxification  
 AU Greene, Jessica F.; Williamson, Kristin C.; Newman, John W.;

Morisseau, Christophe; **Hammock, Bruce D.**

CS Department of Entomology, University of California at Davis, Davis, CA, 95616, USA

SO Archives of Biochemistry and Biophysics (2000), 376(2), 420-432  
CODEN: ABBIA4; ISSN: 0003-9861

PB Academic Press

DT Journal

LA English

CC 4-3 (Toxicology)

Section cross-reference(s): 14

AB **Leukotoxin** (ltx) and isoleukotoxin (iltx) Me esters, are metabolites of Me **linoleic acid**, an essential fatty acid. They have been assocd. with **acute respiratory distress syndrome**. The obsd. toxicity of ltx and iltx is, in fact, due to the metab. of the epoxides to their corresponding **diols** by sol. epoxide hydrolase (sEH). Herein, the authors demonstrate that ltx/iltx are toxic in a time-dependent manner to human sEH expressing cells with a LT50 of 10.6  $\pm$  0.8 h and that ltx and iltx have KM of 6.15  $\pm$  1.0 and 5.17  $\pm$  0.56  $\mu$ M, resp., and Vmax of 2.67  $\pm$  0.04 and 1.86  $\pm$  0.06  $\mu$ mol/min/mg, resp., which can be inhibited by sEH inhibitors. The authors show that four major metabolites of ltx/iltx are formed in their system, including ltx/iltx free acid, ltxd/iltxd, free acid, and phosphatidylcholine and phosphatidylethanolamine contg. the carboxylic acid forms of both ltx/iltx and ltxd/iltxd, but that the only metabolite assocd. with toxicity is the carboxylic acid form of ltxd/iltxd, suggesting the involvement of cellular esterases. The authors demonstrate that a serine esterase inhibitor provides some protection from the toxicity of epoxy fatty esters to sEH expressing cells as do intercellular free sulfhydryls, but that this protection is not due to glutathione conjugation. With these data, the authors have proposed an extension of the metabolic pathway for ltx/iltx in eukaryotic cells. (c) 2000 Academic Press.

ST monoepoxide methyl **linoleate** metab bioactivation toxicity  
detoxification; **leukotoxin diol** epoxide hydrolase  
phospholipid toxicity detoxication

IT Animal cell line

(Sf-21; monoepoxides of me **linoleate** metab. and bioactivation  
and detoxification in relation to **leukotoxin** toxicity)

IT **Respiratory distress syndrome**

(**acute**; monoepoxides of me **linoleate** metab. and  
bioactivation and detoxification in relation to **leukotoxin**  
toxicity)

IT Detoxification

(biol.; monoepoxides of me **linoleate** metab. and bioactivation  
and detoxification in relation to **leukotoxin** toxicity)

IT Phosphatidylcholines, biological studies

Phosphatidylethanolamines, biological studies

Phospholipids, biological studies

RL: ADV (Adverse effect, including toxicity); BSU (Biological study,  
unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM  
(Formation, nonpreparative)

(contg. carboxylic acid forms of both **leukotoxin** and  
isoleukotoxin and **diols**; monoepoxides of me **linoleate**  
metab. and bioactivation and detoxification in relation to  
**leukotoxin** toxicity)

IT Fatty acids, biological studies

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(epoxy, esters; monoepoxides of me **linoleate** metab. and  
bioactivation and detoxification in relation to **leukotoxin**  
toxicity)

IT Epoxides

Epoxides

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)



- (fatty alkyl, carboxy, esters; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT Gene, animal  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(hseH; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT Animal cell  
(human; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT Toxins  
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)  
(**leukotoxins**, **diols**; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT Toxins  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(**leukotoxins**; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT Epoxides  
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(**linoleate**; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT Cell death  
Cytotoxicity  
Enzyme kinetics  
Eukaryote (Eukaryotae)  
Michaelis constant  
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT Thiols (organic), biological studies  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT 9048-63-9, Epoxide hydrolase  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(Sol.; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT 112-63-0D, Methyl **linoleate**, epoxides  
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(mono; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT 2500-59-6 10547-36-1, Methyl isoleukotoxin 21019-43-2, Methyl **leukotoxin** 126639-25-6, **Leukotoxin** A 126639-26-7, Isoleukotoxin 126639-26-7D, Isoleukotoxin, Me esters  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
- IT 60-33-3D, **Linoleic** acid, epoxides, biological studies

RL: ADV (Adverse effect, including toxicity); BPR (Biological process);  
BSU (Biological study, unclassified); BIOL (Biological study); PROC  
(Process)

(monoepoxides of me **linoleate** metab. and bioactivation and  
detoxification in relation to **leukotoxin** toxicity)

IT 73889-55-1, Isoleukotoxin **diol**

RL: ADV (Adverse effect, including toxicity); BSU (Biological study,  
unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM  
(Formation, nonpreparative)

(monoepoxides of me **linoleate** metab. and bioactivation and  
detoxification in relation to **leukotoxin** toxicity)

IT 9001-84-7, Phospholipase A2

RL: ARG (Analytical reagent use); BAC (Biological activity or effector,  
except adverse); BPR (Biological process); BSU (Biological study,  
unclassified); ANST (Analytical study); BIOL (Biological study); PROC  
(Process); USES (Uses)

(monoepoxides of me **linoleate** metab. and bioactivation and  
detoxification in relation to **leukotoxin** toxicity)

IT 37259-58-8, Serine esterase

RL: BAC (Biological activity or effector, except adverse); BPR (Biological  
process); BSU (Biological study, unclassified); BIOL (Biological study);  
PROC (Process)

(monoepoxides of me **linoleate** metab. and bioactivation and  
detoxification in relation to **leukotoxin** toxicity)

IT 70-18-8, Glutathione, biological studies 65095-03-6

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
(Biological study); PROC (Process)

(monoepoxides of me **linoleate** metab. and bioactivation and  
detoxification in relation to **leukotoxin** toxicity)

IT 70-18-8D, Glutathione, conjugates

RL: BPR (Biological process); BSU (Biological study, unclassified); MFM  
(Metabolic formation); BIOL (Biological study); FORM (Formation,  
nonpreparative); PROC (Process)

(monoepoxides of me **linoleate** metab. and bioactivation and  
detoxification in relation to **leukotoxin** toxicity)

IT 141-05-9, Diethyl maleate 92614-59-0, Glutathione ethyl ester

RL: BAC (Biological activity or effector, except adverse); BPR (Biological  
process); BSU (Biological study, unclassified); BIOL (Biological study);  
PROC (Process)

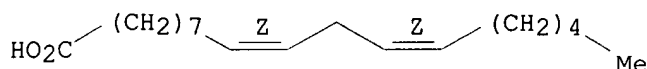
(protection of cells; monoepoxides of me **linoleate** metab. and  
bioactivation and detoxification in relation to **leukotoxin**  
toxicity)

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- IT 60-33-3D, **Linoleic** acid, epoxides, biological studies  
 RL: ADV (Adverse effect, including toxicity); BPR (Biological process);  
 BSU (Biological study, unclassified); BIOL (Biological study); PROC  
 (Process)  
 (monoepoxides of me **linoleate** metab. and bioactivation and  
 detoxification in relation to **leukotoxin** toxicity)
- RN 60-33-3 . HCAPLUS
- CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L69 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:186660 HCAPLUS

DN 133:70547

TI Identification of CYP2C9 as a Human Liver Microsomal **Linoleic**  
Acid Epoxxygenase

AU Draper, Alison J.; Hammock, Bruce D.

CS Department of Chemistry, Bucknell University, Lewisburg, PA, 17837, USA

SO Archives of Biochemistry and Biophysics (2000), 376(1), 199-205

CODEN: ABBIA4; ISSN: 0003-9861

PB Academic Press

DT Journal

LA English

CC 7-3 (Enzymes)

Section cross-reference(s): 15

AB **Leukotoxin** (9,10-epoxy-12-octadecanoate) and isoleukotoxin (12,13-epoxy-9-octadecenoate) are monoepoxides of **linoleic acid**, synthesized by a cytochrome P 450 monooxygenase and possibly by an oxidative burst of inflammatory cells. Recent expts. in this lab. have indicated that the toxicity of **leukotoxin** and isoleukotoxin is not due to these epoxides, but to the 9,10- and 12,13-diol metabolites. **Leukotoxin** and isoleukotoxin are metabolized primarily by the sol. epoxide hydrolase to form **leukotoxin diol**. Investigations with recombinant cytochrome P 450 enzymes have demonstrated that **leukotoxin** and isoleukotoxin can be formed by these enzymes. This study used a combination of exptl. approaches to identify the major cytochrome P 450 enzyme in human liver involved in **linoleic acid** epoxidn. The kinetic parameters were detd.; the Km of **linoleic acid** epoxidn. by pooled human liver microsomes was 170 .mu.M and the Vmax was 58 pmol/mg/min. Correlation anal. was performed using individual samples of human liver microsomes, and the best correlation of **linoleic acid** epoxidn. activity was with tolbutamide hydroxylase activity, CYP2C9. Recombinant CYP2C9 was the most active in **linoleic acid** epoxxygenation, and antibody and chem. inhibition also indicated the importance of CYP2C9. This enzyme, therefore, may serve as a therapeutic target in the treatment of inflammation in order to reduce the amt. of circulating **leukotoxin**/isoleukotoxin and their related **diols**. (c) 2000 Academic Press.

ST cytochrome P450 isoenzyme **linoleate** epoxidn human

IT Epoxidation

Michaelis constant

(identification of CYP2C9 as a human liver microsomal **linoleic**  
acid epoxxygenase)

IT 9035-51-2, Cytochrome P450, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study; unclassified); BIOL (Biological study)

(CYP2C9; identification of CYP2C9 as a human liver microsomal  
**linoleic acid** epoxxygenase)

IT 9048-63-9, Epoxide hydrolase

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study; unclassified); BIOL (Biological study)

(identification of CYP2C9 as a human liver microsomal **linoleic**  
acid epoxxygenase)

IT 60-33-3, **Linoleic Acid**, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)  
(identification of CYP2C9 as a human liver microsomal **linoleic acid epoxygenase**)

IT 73889-55-1, Isoleukotoxin **diol** 126639-25-6, **Leukotoxin**  
126639-26-7, Isoleukotoxin **189191-41-1, Leukotoxin diol**

RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)  
(identification of CYP2C9 as a human liver microsomal **linoleic acid epoxygenase**)

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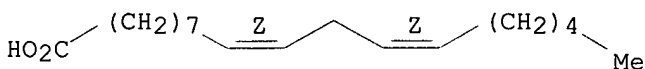
IT 60-33-3, **Linoleic Acid**, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(identification of CYP2C9 as a human liver microsomal **linoleic acid epoxygenase**)

RN 60-33-3 HCAPLUS

CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

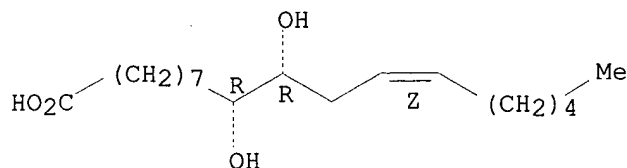


IT 189191-41-1, **Leukotoxin diol**

RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)  
(identification of CYP2C9 as a human liver microsomal **linoleic acid epoxygenase**)

acid epoxxygenase)  
 RN 189191-41-1 HCAPLUS  
 CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.  
 Double bond geometry as shown.



- L69 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2002 ACS  
 AN 2000:158286 HCAPLUS  
 DN 132:318745  
 TI Toxicity of Epoxy Fatty Acids and Related Compounds to Cells Expressing Human Soluble Epoxide Hydrolase  
 AU Greene, Jessica F.; Newman, John W.; Williamson, Kristin C.; Hammock, Bruce D.  
 CS Department of Entomology, University of California at Davis, Davis, CA, 95616, USA  
 SO Chemical Research in Toxicology (2000), 13(4), 217-226  
 CODEN: CRTOEC; ISSN: 0893-228X  
 PB American Chemical Society  
 DT Journal  
 LA English  
 CC 4-3 (Toxicology)  
 AB Sol. epoxide hydrolase (sEH) is suggested to alter the mode of action and increase the toxic potency of fatty acid epoxides. To characterize the structural features necessary for sEH-dependent epoxy fatty acid toxicity, 75 aliph. compds. were **assayed** for cytotoxicity in the presence and absence of sEH. Three groups of aliph. epoxide-**diol** pairs were described by their obsd. differential toxicity. Group I compds. were typified by terminal epoxides whose toxicity was reduced in the presence of sEH. Group II compds. were toxic in either their epoxide or **diol** form, but toxicity was unaffected by sEH. Group III compds. exhibited sEH-dependent toxicity and were therefore used to investigate the structural elements required for cytotoxicity in this study. The optimal structure for group III compds. appeared to be a fatty acid 18-20 atoms long (e.g., a carbon backbone plus a terminal heteroatom) with an epoxide positioned between C-7 and C-12. In the absence of sEH, replacement of epoxides with a vicinal **diol** was required for toxicity. While **diol** stereochem. was unimportant, vicinal **diol**-induced toxicity exhibited fewer positional constraints to toxicity than sEH-dependent epoxide toxicity. Tested fatty acids and esters with neither an epoxide nor a vicinal **diol** were not toxic. These data support the hypothesis that long-chain epoxy fatty acid Me esters are potential pro-toxins metabolized by sEH to more toxic **diols**. Furthermore, our results suggest that the endogenous compds., **leukotoxin** Me ester, 9,10(Z)-epoxyoctadec-12(Z)-enoic acid Me ester, and isoleukotoxin Me ester, 12,13(Z)-epoxyoctadec-9(Z)-enoic acid Me ester, are structurally optimized to elicit the obsd. effect.  
 ST cytotoxicity epoxy fatty acid epoxide hydrolase  
 IT Structure-activity relationship  
 (cytotoxic; toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)  
 IT Mass spectra

- (electrospray ionization; toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)
- IT Fatty acids, biological studies  
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)  
(epoxy; toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)
- IT Epoxides  
Epoxides  
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)  
(fatty alkyl, carboxy; toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)
- IT Cytotoxicity  
Electron ionization mass spectra  
NMR spectroscopy  
Spodoptera frugiperda  
(toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)
- IT 2391-05-1 2566-91-8 2779-85-3 3639-31-4 14936-76-6 17966-13-1  
24560-98-3 29714-26-9 34724-39-5 54635-17-5 54635-18-6  
56687-67-3 61117-79-1 61140-93-0 61177-05-7 70080-20-5  
70116-78-8 73889-55-1 77705-40-9 93635-22-4 99147-53-2  
141724-83-6 152175-57-0 182344-96-3 **189191-41-1**  
265975-94-8 265975-98-2 265976-01-0 265976-08-7 265976-10-1  
265976-15-6 265976-30-5 265976-31-6 265976-32-7 265976-33-8  
265976-34-9 265976-35-0 265976-36-1 265976-37-2 265976-38-3  
265976-40-7  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)
- IT 1041-25-4 6088-36-4 6088-42-2 10547-36-1 21019-43-2 22663-09-8  
52126-87-1 172995-07-2 189191-42-2 265976-22-5 265976-24-7  
265976-26-9 265976-27-0 265976-39-4  
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)  
(toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)
- IT 9048-63-9, Epoxide hydrolase  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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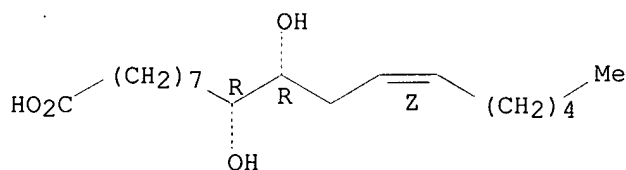
IT 189191-41-1

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
 (toxicity of epoxy fatty acids and related compds. to cells expressing  
 human sol. epoxide hydrolase)

RN 189191-41-1 HCAPLUS

CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX  
 NAME)

Relative stereochemistry.  
 Double bond geometry as shown.



L69 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:110452 HCAPLUS

DN 132:318802

TI **Leukotoxin** and its **diol** induce neutrophil chemotaxis  
 through signal transduction different from that of fMLP

AU Totani, Y.; Saito, Y.; Ishizaki, T.; Sasaki, F.; Ameshima, S.; Miyamori,  
 I.

CS Third Dept of Internal Medicine, Fukui Medical University, Fukui, 910-11,  
 Japan

SO European Respiratory Journal (2000), 15(1), 75-79  
 CODEN: ERJOEI; ISSN: 0903-1936

PB Munksgaard International Publishers Ltd.

DT Journal

LA English

CC 4-5 (Toxicology)

Section cross-reference(s): 14

AB When injected into animals, **leukotoxin** (Lx) causes acute lung  
 injury which is assocd. with neutrophils infiltrating the lung tissues.  
 However, the effect of Lx on neutrophils is still unknown, and recently it  
 has been reported that Lx **diol**, a hydrolyzed metabolite, should  
 be more potent than Lx in vitro. In this study, the authors examd. the



effect of Lx and its **diol** on human neutrophils by assessing their chemotactic response, expression of adhesion mols., and prodn. of peroxides. Both Lx and its **diol** induced chemotaxis in human neutrophils via an involvement of pertussis toxin-sensitive G-proteins, but they did not influence the expression of adhesion mols. or the prodn. of peroxides. Furthermore, Lx synergistically affected chemotaxis with N-formyl-methionyl-leucyl-phenylalanine (fMLP), but not with endothelin 1. Neutrophil chemotaxis induced by both Lx and its **diol** was inhibited by phosphatidylinositol 3-kinase (PI3-K) inhibitors, but not by protein tyrosine kinase (PTK) inhibitors or by protein kinase C (PKC) inhibitors, whereas fMLP-induced chemotaxis was inhibited by PTK inhibitors, but not by PI3-K inhibitors or by PKC inhibitors. These results suggest that neutrophil chemotaxis induced by both Lx and its **diol** involves pathways different from those induced by fMLP. In conclusion, both **leukotoxin** and its **diol** metabolite induce chemotaxis in human neutrophils in an unique way and may act as important bioactive lipids when considering the pathol. mechanism of acute lung injury.

ST **leukotoxin diol** neutrophil chemotaxis signal transduction fMLP

IT Integrins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(antigens CD11b; **leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT Lung, disease

(injury; **leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT Chemotaxis

**Neutrophil**

Signal transduction, biological

(**leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT Peroxides, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(**leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT G proteins (guanine nucleotide-binding proteins)

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(pertussis toxin-sensitive; **leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT Integrins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(.beta.2; **leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT 113972-57-9 189191-41-1, **Leukotoxin diol**

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(**leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT 59880-97-6 80449-02-1, Protein tyrosine kinase 115926-52-8, Phosphatidylinositol 3-kinase 123626-67-5, Endothelin 1 141436-78-4, Protein kinase C

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(**leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD

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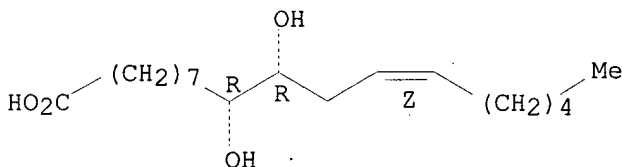
IT 189191-41-1, **Leukotoxin diol**

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
 (leukotoxin and its diol induce neutrophil  
 chemotaxis through signal transduction different from that of fMLP)

RN 189191-41-1 HCAPLUS

CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.  
 Double bond geometry as shown.



<L69 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 1999:503921 HCAPLUS

DN 131:280999

TI Potent urea and carbamate inhibitors of soluble epoxide hydrolases

AU Morisseau, Christophe; Goodrow, Marvin H.; Dowdy, Deanna; Zheng, Jiang; Greene, Jessica F.; Sanborn, James R.; **Hammock, Bruce D.**

CS Department of Entomology, University of California, Davis, CA, 95616, USA

SO Proceedings of the National Academy of Sciences of the United States of America (1999), 96(16), 8849-8854

CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal

LA English

CC 1-3 (Pharmacology)

Section cross-reference(s): 7, 25

AB The sol. epoxide hydrolase (sEH) plays a significant role in the biosynthesis of inflammation mediators as well as xenobiotic transformations. Herein, the authors report the discovery of substituted ureas and carbamates as potent inhibitors of sEH. Some of these selective, competitive tight-binding inhibitors with nanomolar  $K_i$  values interacted stoichiometrically with the homogeneous recombinant murine and human sEHs. These inhibitors enhance cytotoxicity of trans-stilbene oxide, which is active as the epoxide, but reduce cytotoxicity of **leukotoxin**, which is activated by epoxide hydrolase to its toxic

**diol**. They also reduce toxicity of **leukotoxin** in vivo in mice and prevent symptoms suggestive of **acute respiratory distress syndrome**. These potent inhibitors may be valuable tools for testing hypotheses of involvement of **diol** and epoxide lipids in chem. mediation in vitro or in vivo systems.

ST epoxide hydrolase inhibitor urea carbamate structure

IT **Respiratory distress syndrome**

(**adult, acute**; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT Lipids, biological studies

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(diol and epoxide; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT Structure-activity relationship

(enzyme-inhibiting, epoxide hydrolases-inhibiting; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT Toxins

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**leukotoxins**, cytotoxicity; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT Enzyme kinetics

(of inhibition; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 1439-07-2, trans-Stilbene oxide

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(cytotoxicity; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 246165-79-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 57-13-6, Urea, biological studies 64-10-8, N-Phenylurea 102-04-5

102-06-7, N,N'-Diphenylguanidine 102-09-0 538-75-0,  
Dicyclohexylcarbodiimide 603-54-3 611-92-7 612-01-1 623-95-0,  
N,N'-Dipropylurea 722-01-0 1212-29-9, N,N'-Dicyclohexylthiourea  
2387-23-7, N,N'-Dicyclohexylurea 4559-87-9 13074-28-7 20258-07-5  
31510-11-9 36102-06-4 82389-34-2 246165-77-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)

(potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 9048-63-9, Epoxide hydrolase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 2038-57-5, Benzenepropanamine 3173-53-3, Cyclohexylisocyanate

RL: RCT (Reactant); RACT (Reactant or reagent)

(potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L69 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 1999:394294 HCAPLUS

DN 131:168305

TI Effects of **linoleic** acid metabolites on electrical activity in adult rat ventricular myocytes

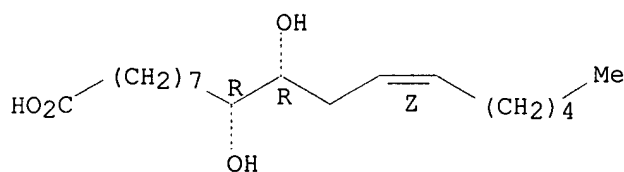
AU Stimers, Joseph R.; Dobretsov, Maxim; Hastings, Stephanie L.; Jude, Anthony R.; Grant, David F.

CS Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

- SO Biochimica et Biophysica Acta (1999), 1438(3), 359-368  
CODEN: BBACAQ; ISSN: 0006-3002
- PB Elsevier Science B.V.
- DT Journal
- LA English
- CC 13-6 (Mammalian Biochemistry)  
Section cross-reference(s): 14
- AB **Leukotoxin (Lx)**, an epoxide deriv. of **linoleic acid**, has been suggested to be a toxic mediator of multiple organ failure in burn patients and of **acute respiratory distress syndrome**. Lx prodn. was recently shown during myocardial ischemia/reperfusion. However, a recent study suggested that to be toxic Lx must be metabolized to Lx-diols. In the present study, isolated adult rat ventricular myocytes were studied with the whole-cell patch-clamp technique to det. the effects of these compds. on cardiac elec. activity. Measurements of action potentials showed that neither **linoleic acid** nor Lx (100  $\mu$ M) caused any significant changes in action potential properties. However, Lx-diols in the range of 10-100  $\mu$ M produced a dose dependent increase in duration and a decrease in overshoot of the action potential. Subsequent voltage clamp expts. isolating Na current (INa) and transient outward K current (Ito) revealed that Lx-diols inhibited INa and Ito by about 80% at 100  $\mu$ M, while **linoleic acid** and Lx had no effect on these currents at the same concn. While Lx-diols produced the same inhibition of INa and Ito at 100  $\mu$ M, its effects were more potent on Ito with significant inhibition at 10  $\mu$ M. Lx-diols also hastened the activation kinetics of Ito but not INa. The action of Lx-diols was rapid (reaching steady state in 3-5 min) and was reversible in 5-10 min following washout. Thus, Lx-diols could favor arrhythmias or cardiac arrest in intact heart and may be responsible for the cardiac problems seen in systemic inflammatory response **syndrome**. These results further support the suggestion that Lx is not toxic in the heart but rather must be metabolized to Lx-diols to produce toxic effects on cardiac muscle.
- ST **linoleate metabolite leukotoxin diol toxic effect heart**
- IT **Heart, disease**  
(arrest; toxic effect of **leukotoxin-diols** on elec. activity of adult rat ventricular myocytes in relation to arrhythmias or cardiac arrest)
- IT **Heart, disease**  
(arrhythmia; toxic effect of **leukotoxin-diols** on elec. activity of adult rat ventricular myocytes in relation to arrhythmias or cardiac arrest)
- IT **Electric potential**  
(biol., action; effects of **linoleic acid** metabolites on elec. activity in adult rat ventricular myocytes)
- IT **Heart**  
(elec. activity; effects of **linoleic acid** metabolites on elec. activity in adult rat ventricular myocytes)
- IT **Toxins**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(**leukotoxins**; effects of **linoleic acid** metabolites on elec. activity in adult rat ventricular myocytes)
- IT **Biological transport**  
(potassium; effects of **linoleic acid** metabolites on elec. activity in adult rat ventricular myocytes)
- IT **Biological transport**  
(sodium; effects of **linoleic acid** metabolites on elec. activity in adult rat ventricular myocytes)
- IT **Heart**  
(ventricle, myocyte; effects of **linoleic acid** metabolites on

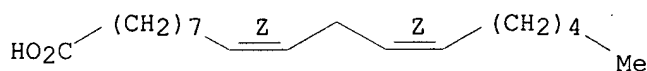
- elec. activity in adult rat ventricular myocytes)
- IT 189191-41-1, **Leukotoxin-diol**  
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
 (effects of **linoleic acid** metabolites on elec.  
 activity in adult rat ventricular myocytes)
- IT 60-33-3, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); BIOL (Biological study)  
 (effects of **linoleic acid** metabolites on elec. activity in  
 adult rat ventricular myocytes)
- IT 7440-09-7, Potassium, biological studies 7440-23-5, Sodium, biological  
 studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
 (Biological study); PROC (Process)  
 (effects of **linoleic acid** metabolites on elec. activity in  
 adult rat ventricular myocytes)
- IT 7440-09-7, Potassium, biological studies 7440-23-5, Sodium, biological  
 studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
 (Biological study); PROC (Process)  
 (transport; effects of **linoleic acid** metabolites on elec.  
 activity in adult rat ventricular myocytes)
- RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
- RE
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- IT 189191-41-1, **Leukotoxin-diol**  
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
 (effects of **linoleic acid** metabolites on elec.  
 activity in adult rat ventricular myocytes)
- RN 189191-41-1 HCAPLUS
- CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX  
 NAME)

Relative stereochemistry.  
 Double bond geometry as shown.



IT 60-33-3, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (effects of **linoleic** acid metabolites on elec. activity in adult rat ventricular myocytes)  
 RN 60-33-3 HCAPLUS  
 CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



69 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:478976 HCAPLUS

DN 129:119888

TI Sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic

IN Bursten, Stuart L.; Federighi, David A.

PA Cell Therapeutics, Inc., USA

SO U.S., 27 pp.

CODEN: USXXAM

DT Patent

LA English

IC ICM G01N033-53

NCL 435007100

CC 9-16 (Biochemical Methods)

Section cross-reference(s): 14, 15

FAN.CNT 1

| PATENT NO. | KIND | DATE     | APPLICATION NO. | DATE     |
|------------|------|----------|-----------------|----------|
| US 5780237 | A    | 19980714 | US 1994-321483  | 19941012 |

AB There is disclosed a diagnostic assay for adult respiratory distress syndrome (ARDS), sepsis, multiple organ dysfunction (MOD) and systemic inflammatory response syndrome (SIRS), comprising (a) measuring the amt. of selected unsatd. free fatty acids (FFAs) and satd. FFAs in a body fluid, and (b) detg. a ratio value comprising the sum of the unsatd. FFAs divided by the sum of the satd. FFAs. There is further disclosed a diagnostic assay for ARDS, sepsis, MOD and SIRS, comprising (a) measuring the amt. of 9- or 13-hydroxyoctadecadienoic acid (HODE) and 5-hydroxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HETE) in a body fluid, and (b) detg. a ratio value of HETE and HODE.

ST sepsis respiration distress syndrome inflammatory diagnostic

IT Fatty acids, analysis

RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)

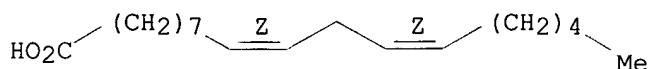
(Satd. free; sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)

IT **Respiratory distress syndrome**

(adult; sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)

- IT Organ, animal  
(dysfunction, multiple; sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
- IT Blood analysis  
Body fluid  
Diagnosis  
Gas chromatography  
HPLC  
Immunoassay  
Saliva  
Sepsis  
Sweat  
TLC (thin layer chromatography)  
Tear (ocular fluid)  
Urine analysis  
(sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
- IT Antibodies  
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)  
(sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
- IT Inflammation  
(systemic inflammatory response syndrome; sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
- IT **Fatty acids, analysis**  
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)  
(unsatd., free; sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
- IT 57-10-3, Hexadecanoic acid, analysis 57-11-4, Octadecanoic acid, analysis 60-33-3, 9,12-Octadecadienoic acid (Z,Z)-, analysis 112-80-1, 9-Octadecenoic acid (Z)-, analysis 506-32-1 544-63-8, Tetradecanoic acid, analysis 18104-45-5 71030-39-2 98524-19-7  
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)  
(sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
- IT 60-33-3, 9,12-Octadecadienoic acid (Z,Z)-, analysis  
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)  
(sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
- RN 60-33-3 HCAPLUS  
CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



- L69 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2002 ACS  
AN 1998:365437 HCAPLUS  
DN 129:36394  
TI In vitro biological effects of leukotoxin and leukotoxin diols on neutrophil  
AU Totani, Yoshitaka; Saito, Yuji; Sasaki, Fumihiko; Miyamori, Isamu; Ishizaki, Takeshi  
CS Third Dep. Intern. Med., Fukui Med. Coll., Japan  
SO Therapeutic Research (1998), 19(4), 1123-1126



CODEN: THREEEL; ISSN: 0289-8020

PB Raifu Saiensu Shuppan K.K.  
 DT Journal  
 LA Japanese  
 CC 1-12 (Pharmacology)  
 Section cross-reference(s): 14

AB **Leukotoxin** and **leukotoxin diols** increased  
 neutrophil chemotaxis but did not affect the expression of adhesion mols.  
 and peroxide prodn. by neutrophil.

ST **leukotoxin diol** neutrophil chemotaxis  
 IT Chemotaxis  
     **Neutrophil**  
     (In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)

IT Cell adhesion molecules  
 Peroxides, biological studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)

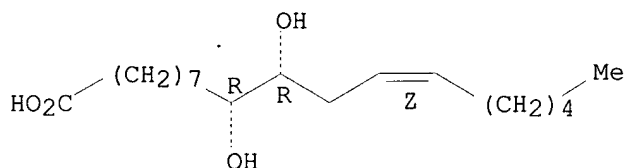
IT Toxins  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (**leukotoxins**; In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)

IT **189191-41-1, Leukotoxin diol**  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)

IT **189191-41-1, Leukotoxin diol**  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)

RN 189191-41-1 HCAPLUS  
 CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.  
 Double bond geometry as shown.



L69 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2002 ACS  
 AN 1998:123974 HCAPLUS  
 DN 128:201056  
 TI Methods of treating **adult respiratory distress syndrome** and other inflammatory diseases mediated by polyunsaturated lipid metabolites, and **assays** for epoxide hydrolase inhibitors

IN **Hammock, Bruce D.**; Moghaddam, Mehran F.; Cheek, Jeffrey M.; Borhan, Babak; Fergusson, James; Grant, David F.; Greene, Jessica F.; Matoba, Kazu; Zheng, Jiang; Sisemore, Marlene F.

PA Regents of the University of California, USA  
 SO PCT Int. Appl., 54 pp.

CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM A01N033-02  
 ICS A01N043-20; A01N043-24; A01N037-02; A61K031-13; A61K031-23;  
 A61K031-335

CC 1-7 (Pharmacology)  
 Section cross-reference(s): 7

FAN.CNT 2

|      | PATENT NO.  | KIND   | DATE     | APPLICATION NO. | DATE     |
|------|---|--|----------|-----------------|----------|
| PI   | WO 9806261  | A1   | 19980219 | WO 1997-US14385 | 19970813 |
|      | W:  | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |          |                 |          |
|      | RW:   | GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG   |          |                 |          |
|      | US 5955496  | A  | 19990921 | US 1997-909523  | 19970812 |
|      | AU 9740692  | A1   | 19980306 | AU 1997-40692   | 19970813 |
|      | EP 926951   | A1   | 19990707 | EP 1997-938335  | 19970813 |
|      | R:  | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI   |          |                 |          |
|      | US 6174695  | B1   | 20010116 | US 1999-312207  | 19990514 |
| PRAI | US 1996-23397P  | P  | 19960813 |                 |          |
|      | US 1997-909523  | A  | 19970812 |                 |          |
|      | WO 1997-US14385   | W  | 19970813 |                 |          |
| AB   | Methods are provided for treating inflammatory diseases mediated by polyunsatd. lipid metabolites by inhibiting epoxide hydrolase. The methods may be used for treating e.g. <b>adult respiratory distress syndrome</b> . Also provided are methods for <b>assaying</b> or screening the epoxide hydrolase inhibitors for inhibitory specificity and for toxicity, as well as novel biol. active THF diols of arachidonic acid, including antibodies thereto. |  |          |                 |          |
| ST   | inflammatory disease treatment epoxide hydrolase inhibitor; polyunsatd lipid metabolite inflammatory disease; screening epoxide hydrolase inhibitor inflammation; <b>ARDS</b> epoxide hydrolase inhibitor   |  |          |                 |          |
| IT   | <b>Respiratory distress syndrome</b><br>( <b>adult</b> ; epoxide hydrolase inhibitors, and screening thereof, for treatment of <b>ARDS</b> and other inflammatory diseases mediated by polyunsatd. lipid metabolites)   |  |          |                 |          |
| IT   | Lipids, biological studies<br>RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)<br>(alkoxides; epoxide hydrolase inhibitors, and screening thereof, for treatment of <b>ARDS</b> and other inflammatory diseases mediated by polyunsatd. lipid metabolites)  |  |          |                 |          |
| IT   | Lung<br>(alveolus, epithelium, cells; epoxide hydrolase inhibitors, and screening thereof, for treatment of <b>ARDS</b> and other inflammatory diseases mediated by polyunsatd. lipid metabolites)  |  |          |                 |          |
| IT   | Nucleic acids<br>RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)<br>(antisense; epoxide hydrolase inhibitors, and screening thereof, for treatment of <b>ARDS</b> and other inflammatory diseases mediated by polyunsatd. lipid metabolites)   |  |          |                 |          |
| IT   | Insect (Insecta)<br>(cell line; epoxide hydrolase inhibitors, and screening thereof, for  |  |          |                 |          |

- treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT Lipids, biological studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)  
 (dihydroxy-; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT Imides  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (diimides, lipophilic; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT **Immunoassay**  
 (enzyme-linked immunosorbent **assay**; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT Animal tissue culture  
 Anti-inflammatory agents  
 Biological transport  
 Drug screening  
 Spodoptera frugiperda  
 Structure-activity relationship  
 (epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT Biological transport  
 (influx, calcium; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT Baculoviridae  
 (insect cell line transfected with; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT Skin  
 (keratinocyte; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT Toxins  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (leukotoxins, metabolites; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT Antibodies  
 RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (to arachidonate THF diol metabolites; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT 6088-36-4, Methyl isoleukotoxin diol 73889-55-1, Isoleukotoxin diol 189191-41-1, **Leukotoxin diol** 189191-42-2, Methyl **leukotoxin diol**  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)
- IT 112-63-0, Methyl **linoleate** 10547-36-1, Methyl isoleukotoxin

21019-43-2, Methyl **leukotoxin** 126639-26-7, Isoleukotoxin  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(epoxide hydrolase inhibitors, and screening thereof, for treatment of  
**ARDS** and other inflammatory diseases mediated by polyunsatd.  
 lipid metabolites)

IT 112-63-0D, Methyl **linoleate**, diepoxides 538-75-0,  
 Dicyclohexylcarbodiimide 1885-07-0D, derivs. 5411-12-1 5411-12-1D,  
 Chalcone oxide, derivs. 5633-36-3 6969-02-4 29425-81-8 32046-97-2  
 32753-95-0 40327-51-3 40327-54-6 40327-57-9 40327-58-0  
 42846-54-8 51477-11-3 203925-63-7 203925-64-8 203925-65-9  
 203925-66-0 203925-67-1 203925-68-2 203925-69-3 203925-70-6  
 203925-71-7 203925-72-8 203925-73-9 203925-74-0 203925-75-1  
 203925-76-2 203925-77-3 203925-78-4 203925-79-5 203925-80-8  
 203925-81-9 203925-82-0 203925-83-1 203925-84-2 203925-85-3

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(epoxide hydrolase inhibitors, and screening thereof, for treatment of  
**ARDS** and other inflammatory diseases mediated by polyunsatd.  
 lipid metabolites)

IT 9048-63-9, Epoxide hydrolase  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(epoxide hydrolase inhibitors, and screening thereof, for treatment of  
**ARDS** and other inflammatory diseases mediated by polyunsatd.  
 lipid metabolites)

IT 506-32-1D, Arachidonic acid, THF diols  
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(epoxide hydrolase inhibitors, and screening thereof, for treatment of  
**ARDS** and other inflammatory diseases mediated by polyunsatd.  
 lipid metabolites)

IT 7440-70-2, Calcium, biological studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(intracellular; epoxide hydrolase inhibitors, and screening thereof,  
 for treatment of **ARDS** and other inflammatory diseases  
 mediated by polyunsatd. lipid metabolites)

IT 506-32-1, Arachidonic acid  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(metabolites; epoxide hydrolase inhibitors, and screening thereof, for  
 treatment of **ARDS** and other inflammatory diseases mediated by  
 polyunsatd. lipid metabolites)

IT 189191-41-1, **Leukotoxin diol**  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

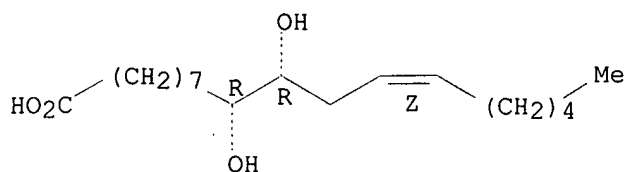
(epoxide hydrolase inhibitors, and screening thereof, for treatment of  
**ARDS** and other inflammatory diseases mediated by polyunsatd.  
 lipid metabolites)

RN 189191-41-1 HCAPLUS

CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

Double bond geometry as shown.



L69 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2002 ACS

AN 1997:297665 HCAPLUS

DN 126:289133

TI Bioactivation of **leukotoxins** to their toxic **diols** by epoxide hydrolase

AU Moghaddam, Mehran F.; Grant, David F.; Cheek, Jeffrey M.; Greene, Jessica F.; Williamson, Kristin C.; **Hammock, Bruce D.**

CS Environ. Stud., DuPont Agric. Pro., Exp. Stn., Wilmington, DE, 19880-0402, USA

SO Nat. Med. (N. Y.) (1997), 3(5), 562-566

CODEN: NAMEFI; ISSN: 1078-8956

PB Nature Publishing Co.

DT Journal

LA English

CC 4-3 (Toxicology)

AB **Leukotoxin** is a **linoleic acid** oxide produced by leukocytes and has been assocd. with the multiple organ failure and **adult respiratory distress syndrome** seen in some severe burn patients. **Leukotoxin** has been reported to be toxic when injected into animals i.v. Herein, the authors report that this lipid is not directly cytotoxic in at least two in vitro systems. Using a baculovirus expression system the authors demonstrate that **leukotoxin** is only cytotoxic in the presence of epoxide hydrolases. In addn., it is the **diol** metabolite that proves toxic to pulmonary alveolar epithelial cells, suggesting a crit. role for the **diol** in **leukotoxin**-assocd. **respiratory** disease. In vivo data also support the toxicity of **leukotoxin diol**. For the first time the authors demonstrate that sol. epoxide hydrolase can bioactivate epoxides to **diols** that are apparently cytotoxic. Thus, **leukotoxin** should be regarded as a protoxin corresponding to the more toxic **diol**. This clearly has implications for designing new clin. interventions.

ST **leukotoxin** bioactivation **diol** epoxide hydrolase

IT Alveolar epithelium (lung)

HeLa cell

Respiratory tract diseases

Spodoptera frugiperda

(bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)

IT 6088-36-4, Methyl isoleukotoxin **diol**

RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation);

BIOL (Biological study); FORM (Formation, nonpreparative)

(Me isoleukotoxin **diol**; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)

IT 10547-36-1, Methyl isoleukotoxin

RL: ADV (Adverse effect, including toxicity); BPR (Biological process);

BIOL (Biological study); PROC (Process)

(Me isoleukotoxin; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)

IT 189191-42-2, Methyl **leukotoxin diol**

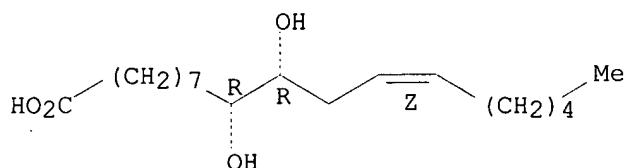
RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation);

BIOL (Biological study); FORM (Formation, nonpreparative)

(Me **leukotoxin diol**; bioactivation of

- leukotoxins to toxic diols by epoxide hydrolase)**
- IT 149405-48-1, Methyl **leukotoxin**  
 RL: ADV (Adverse effect, including toxicity); BPR (Biological process);  
 BIOL (Biological study); PROC (Process)  
 (Me **leukotoxin**; bioactivation of **leukotoxins** to  
 toxic diols by epoxide hydrolase)
- IT 112-63-0, Methyl **linoleate**  
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
 (bioactivation of **leukotoxins** to toxic diols by  
 epoxide hydrolase)
- IT 61949-82-4  
 RL: ADV (Adverse effect, including toxicity); BPR (Biological process);  
 BIOL (Biological study); PROC (Process)  
 (bioactivation of **leukotoxins** to toxic diols by  
 epoxide hydrolase)
- IT 9048-63-9, Epoxide hydrolase  
 RL: BAC (Biological activity or effector, except adverse); BIOL  
 (Biological study)  
 (bioactivation of **leukotoxins** to toxic diols by  
 epoxide hydrolase)
- IT 73889-55-1, Isoleukotoxin **diol**  
 RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation);  
 BIOL (Biological study); FORM (Formation, nonpreparative)  
 (isoleukotoxin **diol**; bioactivation of **leukotoxins**  
 to toxic diols by epoxide hydrolase)
- IT 126639-26-7, Isoleukotoxin  
 RL: ADV (Adverse effect, including toxicity); BPR (Biological process);  
 BIOL (Biological study); PROC (Process)  
 (isoleukotoxin; bioactivation of **leukotoxins** to toxic  
 diols by epoxide hydrolase)
- IT 189191-41-1, Leukotoxin **diol**  
 RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation);  
 BIOL (Biological study); FORM (Formation, nonpreparative)  
 (**leukotoxin diol**; bioactivation of  
**leukotoxins** to toxic diols by epoxide hydrolase)
- IT 189191-41-1, Leukotoxin **diol**  
 RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation);  
 BIOL (Biological study); FORM (Formation, nonpreparative)  
 (**leukotoxin diol**; bioactivation of  
**leukotoxins** to toxic diols by epoxide hydrolase)
- RN 189191-41-1 HCAPLUS
- CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX  
 NAME)

Relative stereochemistry.  
 Double bond geometry as shown.



- L69 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2002 ACS
- AN 1997:161958 HCAPLUS
- TI Study of the mechanism of inhibition of epoxide hydrolases by chalcone  
 oxides.
- AU Morisseau, C.; Du, G.; Newman, J. W.; Nakagawa, Y.; Zheng, J.;  
 Hammock, B. D.
- CS Departments Entomology and Environmental Toxicology, University

California, Davis, CA, 95616, USA  
SO Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), MEDI-126 Publisher: American Chemical Society, Washington, D. C. CODEN: 64AOAA  
DT Conference; Meeting Abstract  
LA English  
AB Metab. of drugs and xenobiotics is among the important factors in detg. the biol. and toxicol. effects of exposure. Many mutagens and carcinogens are degraded by the sol. and microsomal epoxide hydrolases. Conversely, the diol resulting from the hydrolysis of leukotoxin by an epoxide hydrolase is the metabolite responsible for the toxicity of this compd. in cell culture. If prodn. of leukotoxin diol results in the clin. symptoms of ARDS, inhibition of the epoxide hydrolase could reduce symptoms. In this study, we report (1) the quant. anal. of the structure-activity relationship for about forty inhibitors (chalcone oxide derivs.) of sol. epoxide hydrolases, (2) the kinetic study of their action, and (3) the detn. of the structure of the enzyme-inhibitor complex. These results provide an understanding of the mechanism of inhibition permitting the design of therapeutic drug or pro-drug for the treatment of ARDS.

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DICTIONARY FILE UPDATES: 19 JUN 2002 HIGHEST RN 432491-02-6

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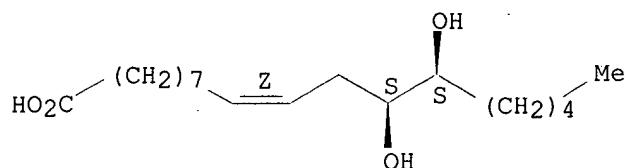
Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> d 171 ide can

L71 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS  
RN 73889-55-1 REGISTRY  
CN 9-Octadecenoic acid, 12,13-dihydroxy-, (9Z,12R,13R)-rel- (9CI) (CA INDEX NAME)  
OTHER CA INDEX NAMES:  
CN 9-Octadecenoic acid, 12,13-dihydroxy-, [R\*,R\*-(Z)]-  
OTHER NAMES:  
CN Isoleukotoxin diol  
FS STEREOSEARCH  
DR 59981-82-7  
MF C18 H34 O4  
LC STN Files: BEILSTEIN\*, CA, CAPLUS, TOXCENTER, USPATFULL  
(\*File contains numerically searchable property data)

Relative stereochemistry.  
Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

12 REFERENCES IN FILE CA (1967 TO DATE)  
12 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:39307  
REFERENCE 2: 133:70547  
REFERENCE 3: 133:69968  
REFERENCE 4: 132:318745  
REFERENCE 5: 128:201056  
REFERENCE 6: 127:230447  
REFERENCE 7: 126:289133  
REFERENCE 8: 124:226704  
REFERENCE 9: 110:172676  
REFERENCE 10: 103:140570

=> d his 171-

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FILE 'REGISTRY' ENTERED AT 17:05:59 ON 21 JUN 2002

FILE 'HCAPLUS' ENTERED AT 17:06:08 ON 21 JUN 2002

FILE 'REGISTRY' ENTERED AT 17:07:30 ON 21 JUN 2002

L71 1 S 73889-55-1

FILE 'HCAPLUS' ENTERED AT 17:07:40 ON 21 JUN 2002

L72 13 S L71  
L73 5 S L72 AND L12-L16  
L74 1 S L72 AND L18-L29  
L75 5 S L73, L74 AND L69  
L76 8 S L72 NOT L75

FILE 'REGISTRY' ENTERED AT 17:08:58 ON 21 JUN 2002

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FILE 'HCAPLUS' ENTERED AT 17:09:11 ON 21 JUN 2002

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FILE LAST UPDATED: 19 Jun 2002 (20020619/ED)

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L75 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:259098 HCAPLUS

DN 133:69968

TI Metabolism of Monoepoxides of Methyl **Linoleate**: Bioactivation and Detoxification

AU Greene, Jessica F.; Williamson, Kristin C.; **Newman, John W.**; Morisseau, Christophe; **Hammock, Bruce D.**

CS Department of Entomology, University of California at Davis, Davis, CA, 95616, USA

SO Archives of Biochemistry and Biophysics (2000), 376(2), 420-432  
CODEN: ABBIA4; ISSN: 0003-9861

PB Academic Press

DT Journal

LA English

AB **Leukotoxin** (ltx) and isoleukotoxin (iltx) Me esters, are metabolites of Me **linoleic acid**, an essential fatty acid. They have been assocd. with **acute respiratory distress syndrome**. The obsd. toxicity of ltx and iltx is, in fact, due to the metab. of the epoxides to their corresponding **diols** by sol. epoxide hydrolase (sEH). Herein, the authors demonstrate that ltx/iltx are toxic in a time-dependent manner to human sEH expressing cells with a LT50 of 10.6 +/- 0.8 h and that ltx and iltx have KM of 6.15 +/- 1.0 and 5.17 +/- 0.56 .mu.M, resp., and Vmax of 2.67 +/- 0.04 and 1.86 +/- 0.06 .mu.mol/min/mg, resp., which can be inhibited by sEH inhibitors. The authors show that four major metabolites of ltx/iltx are formed in their system, including ltx/iltx free acid, ltxd/iltxd, free acid, and phosphatidylcholine and phosphatidylethanolamine contg. the carboxylic acid forms of both ltx/iltx and ltxd/iltxd, but that the only metabolite assocd. with toxicity is the carboxylic acid form of ltxd/iltxd, suggesting the involvement of cellular esterases. The authors demonstrate that a serine esterase inhibitor provides some protection from the toxicity of epoxy fatty esters to sEH expressing cells as do intercellular free sulfhydryls, but that this protection is not due to glutathione conjugation. With these data, the authors have proposed an extension of the metabolic pathway for ltx/iltx in eukaryotic cells. (c) 2000 Academic Press.

IT 60-33-3D, **Linoleic acid**, epoxides, biological studies

RL: ADV (Adverse effect, including toxicity); BPR (Biological process);  
BSU (Biological study, unclassified); BIOL (Biological study); PROC  
(Process)

(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 73889-55-1, Isoleukotoxin diol

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L75 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:186660 HCAPLUS

DN 133:70547

TI Identification of CYP2C9 as a Human Liver Microsomal **Linoleic** Acid Epoxxygenase

AU Draper, Alison J.; **Hammock, Bruce D.**

CS Department of Chemistry, Bucknell University, Lewisburg, PA, 17837, USA

SO Archives of Biochemistry and Biophysics (2000), 376(1), 199-205

CODEN: ABBIA4; ISSN: 0003-9861

PB Academic Press

DT Journal

LA English

AB **Leukotoxin** (9,10-epoxy-12-octadecanoate) and isoleukotoxin (12,13-epoxy-9-octadecenoate) are monoepoxides of **linoleic acid**, synthesized by a cytochrome P 450 monooxygenase and possibly by an oxidative burst of inflammatory cells. Recent expts. in this lab. have indicated that the toxicity of **leukotoxin** and isoleukotoxin is not due to these epoxides, but to the 9,10- and 12,13-**diol** metabolites. **Leukotoxin** and isoleukotoxin are metabolized primarily by the sol. epoxide hydrolase to form **leukotoxin diol**. Investigations with recombinant cytochrome P 450 enzymes have demonstrated that **leukotoxin** and isoleukotoxin can be formed by these enzymes. This study used a combination of exptl. approaches to identify the major cytochrome P 450 enzyme in human liver involved in **linoleic acid** epoxidn. The kinetic parameters were detd.; the Km of **linoleic acid** epoxidn. by pooled human liver microsomes was 170 .mu.M and the Vmax was 58 pmol/mg/min. Correlation anal. was performed using individual samples of human liver microsomes, and the best correlation of **linoleic acid** epoxidn. activity was with tolbutamide hydroxylase activity, CYP2C9. Recombinant CYP2C9 was the most active in **linoleic acid** epoxxygenation, and antibody and chem. inhibition also indicated the importance of CYP2C9. This enzyme, therefore, may serve as a therapeutic target in the treatment of inflammation in order to reduce the amt. of circulating **leukotoxin**/isoleukotoxin and their related **diols**. (c) 2000 Academic Press.

IT 60-33-3, **Linoleic** Acid, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(identification of CYP2C9 as a human liver microsomal **linoleic** acid epoxxygenase)

IT 73889-55-1, Isoleukotoxin diol 189191-41-1, **Leukotoxin diol**

RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(identification of CYP2C9 as a human liver microsomal **linoleic** acid epoxxygenase)

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L75 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:158286 HCAPLUS

DN 132:318745  
TI Toxicity of Epoxy Fatty Acids and Related Compounds to Cells Expressing Human Soluble Epoxide Hydrolase  
AU Greene, Jessica F.; Newman, John W.; Williamson, Kristin C.; Hammock, Bruce D.  
CS Department of Entomology, University of California at Davis, Davis, CA, 95616, USA  
SO Chemical Research in Toxicology (2000), 13(4), 217-226  
CODEN: CRTOEC; ISSN: 0893-228X  
PB American Chemical Society  
DT Journal  
LA English  
AB Sol. epoxide hydrolase (sEH) is suggested to alter the mode of action and increase the toxic potency of fatty acid epoxides. To characterize the structural features necessary for sEH-dependent epoxy fatty acid toxicity, 75 aliph. compds. were **assayed** for cytotoxicity in the presence and absence of sEH. Three groups of aliph. epoxide-**diol** pairs were described by their obsd. differential toxicity. Group I compds. were typified by terminal epoxides whose toxicity was reduced in the presence of sEH. Group II compds. were toxic in either their epoxide or **diol** form, but toxicity was unaffected by sEH. Group III compds. exhibited sEH-dependent toxicity and were therefore used to investigate the structural elements required for cytotoxicity in this study. The optimal structure for group III compds. appeared to be a fatty acid 18-20 atoms long (e.g., a carbon backbone plus a terminal heteroatom) with an epoxide positioned between C-7 and C-12. In the absence of sEH, replacement of epoxides with a vicinal **diol** was required for toxicity. While **diol** stereochem. was unimportant, vicinal **diol**-induced toxicity exhibited fewer positional constraints to toxicity than sEH-dependent epoxide toxicity. Tested fatty acids and esters with neither an epoxide nor a vicinal **diol** were not toxic. These data support the hypothesis that long-chain epoxy fatty acid Me esters are potential pro-toxins metabolized by sEH to more toxic **diols**. Furthermore, our results suggest that the endogenous compds., **leukotoxin** Me ester, 9,10(Z)-epoxyoctadec-12(Z)-enoic acid Me ester, and **isoleukotoxin** Me ester, 12,13(Z)-epoxyoctadec-9(Z)-enoic acid Me ester, are structurally optimized to elicit the obsd. effect.  
IT 73889-55-1 189191-41-1  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)  
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L75 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2002 ACS  
AN 1998:123974 HCAPLUS  
DN 128:201056  
TI Methods of treating **adult respiratory distress syndrome** and other inflammatory diseases mediated by polyunsaturated lipid metabolites, and **assays** for epoxide hydrolase inhibitors  
IN Hammock, Bruce D.; Moghaddam, Mehran F.; Cheek, Jeffrey M.; Borhan, Babak; Fergusson, James; Grant, David F.; Greene, Jessica F.; Matoba, Kazu; Zheng, Jiang; Sisemore, Marlene F.  
PA Regents of the University of California, USA  
SO PCT Int. Appl., 54 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 2

| PATENT NO. | KIND | DATE  | APPLICATION NO. | DATE  |
|------------|------|-------|-----------------|-------|
| -----      | ---- | ----- | -----           | ----- |

PI WO 9806261 A1 19980219 WO 1997-US14385 19970813  
 W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG  
 US 5955496 A 19990921 US 1997-909523 19970812  
 AU 9740692 A1 19980306 AU 1997-40692 19970813  
 EP 926951 A1 19990707 EP 1997-938335 19970813  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI  
 US 6174695 B1 20010116 US 1999-312207 19990514  
 PRAI US 1996-23397P P 19960813  
 US 1997-909523 A 19970812  
 WO 1997-US14385 W 19970813  
 AB Methods are provided for treating inflammatory diseases mediated by polyunsatd. lipid metabolites by inhibiting epoxide hydrolase. The methods may be used for treating e.g. **adult respiratory distress syndrome**. Also provided are methods for **assaying** or screening the epoxide hydrolase inhibitors for inhibitory specificity and for toxicity, as well as novel biol. active THF diols of arachidonic acid, including antibodies thereto.  
 IT 73889-55-1, Isoleukotoxin diol 189191-41-1,  
**Leukotoxin diol**  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)  
 L75 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2002 ACS  
 AN 1997:297665 HCAPLUS  
 DN 126:289133  
 TI Bioactivation of **leukotoxins** to their toxic **diols** by epoxide hydrolase  
 AU Moghaddam, Mehran F.; Grant, David F.; Cheek, Jeffrey M.; Greene, Jessica F.; Williamson, Kristin C.; **Hammock, Bruce D.**  
 CS Environ. Stud., DuPont Agric. Pro., Exp. Stn., Wilmington, DE, 19880-0402, USA  
 SO Nat. Med. (N. Y.) (1997), 3(5), 562-566  
 CODEN: NAMEFI; ISSN: 1078-8956  
 PB Nature Publishing Co.  
 DT Journal  
 LA English  
 AB **Leukotoxin** is a **linoleic acid** oxide produced by leukocytes and has been assocd. with the multiple organ failure and **adult respiratory distress syndrome** seen in some severe burn patients. **Leukotoxin** has been reported to be toxic when injected into animals i.v. Herein, the authors report that this lipid is not directly cytotoxic in at least two in vitro systems. Using a baculovirus expression system the authors demonstrate that **leukotoxin** is only cytotoxic in the presence of epoxide hydrolases. In addn., it is the **diol** metabolite that proves toxic to pulmonary alveolar epithelial cells, suggesting a crit. role for the **diol** in **leukotoxin**-assocd. **respiratory** disease. In vivo data also support the toxicity of **leukotoxin diol**. For the first time the authors demonstrate that sol. epoxide hydrolase can bioactivate epoxides to **diols** that are apparently cytotoxic. Thus, **leukotoxin** should be regarded as a

protoxin corresponding to the more toxic diol. This clearly has implications for designing new clin. interventions.

IT 73889-55-1, Isoleukotoxin diol

RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative) (isoleukotoxin diol; bioactivation of leukotoxins to toxic diols by epoxide hydrolase)

IT 189191-41-1, Leukotoxin diol

RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative) (leukotoxin diol; bioactivation of leukotoxins to toxic diols by epoxide hydrolase)

=> fil biosis

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CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 19 June 2002 (20020619/ED)

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L96 ANSWER 1 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2002:289566 BIOSIS

DN PREV200200289566

TI Effects of linoleic acid metabolites on cardiac Na<sup>+</sup> current.

AU Harrell, Maddison D. (1); Stimers, Joseph R.

CS (1) Tulane University, New Orleans, LA USA

SO Biophysical Journal, (January, 2002) Vol. 82, No. 1 Part 2, pp. 87a.

<http://intl.biophysj.org/>. print.

Meeting Info.: 46th Annual Meeting of the Biophysical Society San

Francisco, California, USA February 23-27, 2002

ISSN: 0006-3495.

DT Conference

LA English

CC General Biology - Symposia, Transactions and Proceedings of

Conferences, Congresses, Review Annuals \*00520

Cytology and Cytochemistry - Animal \*02506

Biophysics - Membrane Phenomena \*10508

Cardiovascular System - Physiology and Biochemistry \*14504

IT Major Concepts

Cardiovascular System (Transport and Circulation); Membranes (Cell Biology)

IT Parts, Structures, & Systems of Organisms

ventricular myocytes: circulatory system

IT Chemicals & Biochemicals

9,10-dihydroxy-12-octadecenoic acid; 9,10-dihydroxy-12-octadecenoic acid ester; 9,10-epoxy-12-octadecenoic acid; 9,10-epoxy-12-octadecenoic acid ester; linoleic acid metabolites

IT Miscellaneous Descriptors

cardiac sodium ion current; Meeting Abstract; Meeting Poster

ORGN Super Taxa

Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name

rat (Muridae)

ORGN Organism Superterms

Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

RN 53734-70-6 (9,10-DIHYDROXY-12-OCTADECENOIC ACID)

L96 ANSWER 2 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2001:250820 BIOSIS

DN PREV200100250820

TI Linoleic acid-derived epoxides alter calcium and nitric oxide metabolism in endothelial cells.

AU Saraswathi, V. (1); Narayan, P. (1); Hammock, B. D.; Meerarani, P. (1); Toborek, M. (1); Hennig, B. (1)

CS (1) University of Kentucky, Lexington, KY, 40506-0054 USA

SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A190. print.

Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA

March 31-April 04, 2001

ISSN: 0892-6638.

DT Conference

LA English

SL English

AB Several lines of evidence suggest that increased intake of linoleic acid (LA), the predominant polyunsaturated fatty acid in Western diets, can cause vascular endothelial cell (EC) activation. The toxic effects of LA may be mediated by its epoxide metabolites **leukotoxin** (LTX) and **leukotoxin diol** (LTXD). Both (Ca<sup>2+</sup>)<sub>i</sub> and NO are critical regulators of normal/abnormal functions of the vasculature. We investigated whether LA and its metabolites can modify (Ca<sup>2+</sup>)<sub>i</sub> and NO levels in porcine artery EC. LA treatment increased (Ca<sup>2+</sup>)<sub>i</sub> after 3 h of exposure. In contrast, LTX or LTXD increased (Ca<sup>2+</sup>)<sub>i</sub> within minutes. Similar to the effects on (Ca<sup>2+</sup>)<sub>i</sub>, both LTX and its **diol** metabolite increased the formation of NO more rapidly than LA, as observed by an increase in DAF-2 fluorescence. However, the increase in NO was observed later than the rise in (Ca<sup>2+</sup>)<sub>i</sub>, thereby suggesting the calcium dependency of eNOS activation. Excessive (Ca<sup>2+</sup>)<sub>i</sub> and NO formation may lead to increased oxidative stress. EC exposure to both LA and its epoxide metabolites increased NF-kappaB activation. Our data suggest that LA metabolites contribute markedly to EC activation, possibly mediated through altered (Ca<sup>2+</sup>)<sub>i</sub> and NO metabolism and a resulting alterations in EC redox status.

CC Biochemical Studies - Minerals \*10069

General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals \*00520

Cytology and Cytochemistry - Animal \*02506

Biochemical Studies - General \*10060

Biochemical Studies - Lipids \*10066

Metabolism - General Metabolism; Metabolic Pathways \*13002

Nutrition - General Studies, Nutritional Status and Methods \*13202

Cardiovascular System - Physiology and Biochemistry \*14504

BC Suidae 85740

IT Major Concepts

Metabolism; Nutrition; Cardiovascular System (Transport and Circulation)

IT Parts, Structures, & Systems of Organisms

vascular endothelial cell: circulatory system, redox status

IT Chemicals & Biochemicals

calcium(II) ion: intracellular, metabolism; fatty acid: metabolism;

linoleic acid-derived epoxides; nitric oxide: metabolism

IT Miscellaneous Descriptors

Western diet; Meeting Abstract

ORGN Super Taxa

Suidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name

porcine (Suidae)

ORGN Organism Superterms

Animals; Artiodactyls; Chordates; Mammals; Nonhuman Mammals; Nonhuman

Vertebrates; Vertebrates  
RN 14127-61-8 (CALCIUM(II) ION)  
10102-43-9 (NITRIC OXIDE)

L96 ANSWER 3 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 1999:406235 BIOSIS  
DN **PREV199900406235**  
TI **Leukotoxins** and the lung.  
AU Ishizaki, T. (1); Ozawa, T.; Voelkel, N. F.  
CS (1) Department of Internal Medicine, Fukui Medical University, Fukui,  
910-11 Japan  
SO Pulmonary Pharmacology & Therapeutics, (1999) Vol. 12, No. 3, pp. 145-155.  
ISSN: 1094-5539.  
DT General Review  
LA English  
CC Toxicology - General; Methods and Experimental \*22501  
Biochemical Studies - General \*10060  
Biophysics - General Biophysical Studies \*10502  
Respiratory System - General; Methods \*16001  
BC Hominidae 86215  
Muridae 86375  
IT Major Concepts  
Respiratory System (Respiration); Toxicology  
IT Parts, Structures, & Systems of Organisms  
lung: respiratory system; pulmonary cells: respiratory system;  
pulmonary vessels: respiratory system  
IT Diseases  
lung injury: **leukotoxin**-induced, respiratory system disease  
IT Chemicals & Biochemicals  
eNOS [endothelial nitric oxide synthase]; iNOS [inducible nitric oxide  
synthase]; **leukotoxin diol**: **leukotoxin**  
epoxide hydrolase-metabolite; **leukotoxin**: cytotoxicity,  
linoleate epoxide; oxygen radicals: production; superoxide: production  
ORGN Super Taxa  
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae:  
Rodentia, Mammalia, Vertebrata, Chordata, Animalia  
ORGN Organism Name  
human (Hominidae); rat (Muridae)  
ORGN Organism Superterms  
Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman  
Vertebrates; Primates; Rodents; Vertebrates  
RN 113972-57-9 (**LEUKOTOXIN**)  
189191-41-1 (**LEUKOTOXIN DIOL**)  
11062-77-4 (OXYGEN RADICALS)  
11062-77-4 (SUPEROXIDE)

L96 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 1998:202955 BIOSIS  
DN PREV199800202955  
TI **Leukotoxin-diol** produces greater acute lung injury in  
mice than does **leukotoxin**.  
AU Zheng, J.; Plopper, C.; Hammock, B.  
CS Univ. Calif., Davis, CA 95616 USA  
SO FASEB Journal, (March 20, 1998) Vol. 12, No. 5, pp. A787.  
Meeting Info.: Annual Meeting of the Professional Research Scientists on  
Experimental Biology 98, Part II San Francisco, California, USA April  
18-22, 1998 Federation of American Societies for Experimental Biology  
. ISSN: 0892-6638.  
DT **Conference**  
LA English  
CC Toxicology - General; Methods and Experimental \*22501  
Metabolism - General Metabolism; Metabolic Pathways \*13002  
Respiratory System - Pathology \*16006

**General Biology - Symposia, Transactions and Proceedings of  
Conferences, Congresses, Review Annuals \*00520**

BC Muridae 86375  
IT Major Concepts  
Metabolism; Respiratory System (Respiration); Toxicology  
IT Diseases  
acute lung injury: injury, respiratory system disease  
IT Chemicals & Biochemicals  
leukotoxin-diol: toxicity; leukotoxin:  
toxicity; linoleic acid  
IT Miscellaneous Descriptors  
Meeting Abstract  
ORGN Super Taxa  
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia  
ORGN Organism Name  
mouse (Muridae)  
ORGN Organism Superterms  
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates;  
Rodents; Vertebrates  
RN 113972-57-9 (LEUKOTOXIN)  
60-33-3 (LINOLEIC ACID)

~~L96~~ ANSWER 5 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1996:125460 BIOSIS  
DN PREV199698697595  
TI Glucuronic acid-conjugated dihydroxy fatty acids in the urine of patients  
with generalized peroxisomal disorders.  
AU Street, Jacqueline M. (1); Evans, James E.; Natowicz, Marvin R.  
CS (1) E.K. Shriver Center, 200 Trapelo Rd., Waltham, MA 02254 USA  
SO Journal of Biological Chemistry, (1996) Vol. 271, No. 7, pp. 3507-3516.  
ISSN: 0021-9258.  
DT Article  
LA English  
AB Urine extracts from children diagnosed with generalized peroxisomal  
disorders were screened by continuous flow-negative ion fast atom  
bombardment-mass spectrometry. In 45 of 60 children with generalized  
peroxisomal disorders, we observed one or more intense ions (m/z 489, 505,  
461, and others) that are infrequently found in children with cholestatic  
liver disease or normal children. Compounds giving rise to these ions were  
isolated using reverse phase and anion exchange chromatography. After  
appropriate derivatization and/or methanolysis the compounds were analyzed  
using capillary gas chromatography-mass spectrometry. The major compounds  
were found to be 12,13-dihydroxy-9-octadecenoic acid and  
9,10-dihydroxy-12-octadecenoic acid, with one of the hydroxyl groups in  
glycosidic linkage with glucuronic acid. Minor compounds were glucuronic  
acid conjugates of 9,10-dihydroxy-octadecanoic acid, and  
12,13-dihydroxy-6,9-, 15,16-dihydroxy-9,12-, and 9,10-dihydroxy-12,15-  
octadecadienoic acids. A series of hexadecanoic, hexadecenoic, and  
hexadecadienoic acid glucuronides which appear to be beta-oxidation  
products of the C18 fatty acids were also observed, with the major species  
being 10,11-dihydroxy-7-hexadecenoic acid glucuronide. In all, 16 C 16 and  
C 18 dihydroxy fatty acids were identified by gas chromatography-mass  
spectrometry. A series of at least 11 trihydroxy fatty acids was also  
observed but not fully characterized. Measurement of these compounds may  
prove to be useful in the diagnosis of some peroxisomal disorders.  
CC Genetics and Cytogenetics - Human \*03508  
Clinical Biochemistry; General Methods and Applications \*10006  
Biochemical Studies - Lipids \*10066  
Pathology, General and Miscellaneous - Diagnostic \*12504  
Metabolism - Lipids \*13006  
Metabolism - Metabolic Disorders \*13020  
Digestive System - Pathology \*14006  
Urinary System and External Secretions - Physiology and Biochemistry



\*15504  
BC Hominidae \*86215  
IT Major Concepts  
Biochemistry and Molecular Biophysics; Clinical Chemistry (Allied Medical Sciences); Gastroenterology (Human Medicine, Medical Sciences); Genetics; Metabolism; Pathology; Urinary System (Chemical Coordination and Homeostasis)  
IT Chemicals & Biochemicals  
GLUCURONIC ACID; 12,13-DIHYDROXY-9-OCTADECENOIC ACID;  
9,10-DIHYDROXY-12-OCTADECENOIC ACID; 9,10-DIHYDROXY-OCTADECANOIC ACID  
IT Miscellaneous Descriptors  
CHILDREN; CHOLESTATIC LIVER DISEASE; DIAGNOSIS; TRIHYDROXY FATTY ACIDS;  
12,13-DIHYDROXY-6,9-OCTADECADIENOIC ACID; 12,13-DIHYDROXY-9-OCTADECENOIC ACID; 15,16-DIHYDROXY-9,12-OCTADECADIENOIC ACID;  
9,10-DIHYDROXY-OCTADECANOIC ACID; 9,10-DIHYDROXY-12-OCTADECENOIC ACID;  
9,10-DIHYDROXY-12,15-OCTADECADIENOIC ACID  
ORGN Super Taxa  
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia  
ORGN Organism Name  
human (Hominidae)  
ORGN Organism Superterms  
animals; chordates; humans; mammals; primates; vertebrates  
RN 576-37-4Q (GLUCURONIC ACID)  
6556-12-3Q (GLUCURONIC ACID)  
53734-71-7 (12,13-DIHYDROXY-9-OCTADECENOIC ACID)  
53734-70-6 (9,10-DIHYDROXY-12-OCTADECENOIC ACID)  
120-87-6 (9,10-DIHYDROXY-OCTADECANOIC ACID)

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=> d all abeq tech tot

L110 ANSWER 1 OF 2 WPIX (C) 2002 THOMSON DERWENT  
AN 2000-543662 [49] WPIX  
CR 1998-159182 [14]  
DNC C2000-161838  
TI Epoxide hydrolase inhibitors useful for treating inflammation and in  
conjunction with cancer therapy.  
DC B05 C03  
IN GOODROW, M H; HAMMOCK, B D; MORISSEAU, C H; SANBORN, J;

SEVERSON, T; ZHENG, J  
 PA (REGC) UNIV CALIFORNIA  
 CYC 90  
 PI WO 2000048593 A1 20000824 (200049)\* EN 40p A61K031-317  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
 OA PT SD SE SL SZ TZ UG ZW  
 W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES  
 FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS  
 LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL  
 TJ TM TR TT TZ UA UG UZ VN YU ZA ZW  
 AU 2000033608 A 20000904 (200103) A61K031-317  
 EP 1154764 A1 20011121 (200176) EN A61K031-00  
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
 RO SE SI  
 ADT WO 2000048593 A1 WO 2000-US3495 20000210; AU 2000033608 A AU 2000-33608  
 20000210; EP 1154764 A1 EP 2000-911767 20000210, WO 2000-US3495 20000210  
 FDT AU 2000033608 A Based on WO 200048593; EP 1154764 A1 Based on WO 200048593  
 PRAI US 1999-252148 19990218  
 IC ICM A61K031-00; A61K031-317  
 AB WO 200048593 A UPAB: 20011227  
 NOVELTY - Biologically stable inhibitors of soluble epoxide hydrolases  
 used to selectively inhibit epoxide hydrolase in therapeutic and  
 agricultural applications.  
 DETAILED DESCRIPTION - Treating an epoxide hydrolase, useful to  
 purify, isolate, or inhibit the epoxide hydrolase comprises providing a  
 carbonyl compound of formula (I) in free form or being derivatized so as  
 to be immobilized to a water insoluble support; and contacting the free  
 form or immobilized compound with an epoxide hydrolase under conditions in  
 which the epoxide hydrolase is enzymatically active, the contacting  
 effective to form a complex between the compound and the epoxide  
 hydrolase, in which the activity of the epoxide hydrolase so complexed is  
 modified with respect to enzymatically active, uncomplexed epoxide  
 hydrolase.  
 X = N, O, S or C;  
 Y' = N, O or S  
 at least one of R1-R4 = H; provided that R2 = H when X = N but R2 is  
 not present when X = S or O; and R4 = H when Y' = N but R4 is not present  
 when Y' = S or O;  
 R1, R3 = H, 1-20C alkyl, cycloalkyl, aryl, acyl or heterocyclyl.  
 INDEPENDENT CLAIMS are included for:  
 (1) a purification method for an epoxide hydrolase comprising  
 immobilizing (II) to a water-insoluble support; and eluting an aqueous  
 solution having an epoxide hydrolase in it through the support; and  
 (2) an affinity separations article comprising a water insoluble  
 support defining an exposed surface and having an immobilized compound on  
 it, the immobilized compound being derived from (I), and the compound  
 being derivatized for immobilization through one of R1 or R3, the  
 immobilized compound being capable of forming a complex with an epoxide  
 hydrolase.  
 Z = O or S;  
 W' = C or S;  
 R1', R3' = 1-20C alkyl, cycloalkyl, aryl, acyl, heterocyclyl.  
 ACTIVITY - Antiinflammatory; respiratory; cytostatic;  
 immunosuppressive; antibacterial; gastrointestinal; tranquilizer;  
 vulnerary; hemostatic; antipyretic; hypotensive. Male Swiss Webster mice  
 were pretreated i.p. with dicyclohexylurea suspended in corn oil (400  
 mg/kg) or corn oil as positive controls. After 30 minutes of the  
 pretreatment, the mice were treated intravenously through the tail vein  
 with a 1:1 mixture of **leukotoxin**/isoleutotoxin methyl esters in  
 ethanol. The mice died of respiratory distress after exposure to  
**leukotoxin/isoleukotoxin**. However, pretreatment with  
 N,N'-dicyclohexyl-urea either blocked the animal death or lengthened the  
 lives of the mice. IC50 of (I) is less than 500 micro M (claimed).

## MECHANISM OF ACTION - Epoxide-hydrolase inhibitor.

USE - (I) are epoxide hydrolase inhibitors useful for the treatment of inflammation e.g. adult respiratory distress syndrome or in conjunction with a cancer therapy. (I) may also be used for treating sepsis, pancreatitis, multiple trauma such as brain injury, hemorrhagic shock, immune-mediated organ injury, fever and hypertension. The method is useful for inhibiting an insect epoxide hydrolase, fungal epoxide hydrolase or to reduce mycotoxic production by fungi; for purifying or isolating a microsomal epoxide hydrolase (the compound is derivatized so as to be immobilized to a water insoluble support); for inhibiting a mammalian soluble or microsomal epoxide hydrolase; and for inhibiting a plant epoxide hydrolase.

ADVANTAGE - (I) are biologically stable.

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: B10-A11A; B10-A11B; B10-A12A; B10-A12B; B10-A12C; B10-A13B; B14-A01; B14-C03; B14-C04; B14-E10; B14-F02B; B14-G02; B14-H01; B14-J01B4; B14-K01; C10-A11A; C10-A11B; C10-A12A; C10-A12B; C10-A12C; C10-A13B; C14-A01; C14-C03; C14-C04; C14-E10; C14-F02B; C14-G02; C14-H01; C14-J01B4; C14-K01

TECH UPTX: 20001006

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: The first step includes converting a precursor form of the compound before forming the complex. The precursor form of the compound is a carbodiimine or thiourea. The compound is capable of establishing anionic bond with a carboxylic acid residue of a protein, to stabilize one or more hydrogen bonds or to have a group able to establish a hydrogen bond with a tyrosine residue over the catalytic site. The modified activity of the epoxide hydrolase when in the complex is epoxide hydrolase inhibition. The epoxide hydrolase of the complex is selectively formed with a soluble epoxide hydrolase. The compound reduces the conversion of lipid epoxides to the corresponding diols. The compound is provided in combination with a plant growth regulator, a herbicide, an insect growth regulator, an insecticide or a fungicide.

L110 ANSWER 2 OF 2 WPIX (C) 2002 THOMSON DERWENT

AN 1998-159182 [14] WPIX

CR 2000-543662 [47]

DNC C1998-051324

TI Treating inflammatory disease with inhibitor of epoxy hydrolase - to prevent formation of pro-inflammatory diol metabolites of fatty acids, also new di ol(s) and antibodies against them, particularly for adult respiratory distress syndrome.

DC B04 B05 D16

IN BORHAN, B; CHEEK, J M; FERGUSON, J; GRANT, D F; GREENE, J F; HAMMOCK, B D; MATOBA, K; MOGHADDAM, M F; SISEMORE, M F; ZHENG, J; GOODROW, M H; MORISSEAU, C H; SANBORN, J; SEVERSON, T

PA (REGC) UNIV CALIFORNIA

CYC 79

PI WO 9806261 A1 19980219 (199814)\* EN 53p A01N033-02

RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

AU 9740692 A 19980306 (199830)

EP 926951 A1 19990707 (199931) EN

R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

US 5955496 A 19990921 (199945) A61K031-34

US 6150415 A 20001121 (200101) A61K031-17

US 6174695 B1 20010116 (200106) C12Q001-34

ADT WO 9806261 A1 WO 1997-US14385 19970813; AU 9740692 A AU 1997-40692 19970813; EP 926951 A1 EP 1997-938335 19970813, WO 1997-US14385 19970813; US 5955496 A Provisional US 1996-23397P 19960813, US 1997-909523 19970812; US 6150415 A Provisional US 1996-23397P 19960813, CIP of US 1997-909523 19970812, US 1999-252148 19990218; US 6174695 B1 Provisional US 1996-23397P 19960813, Div ex US 1997-909523 19970812, US 1999-312207 19990514

FDT AU 9740692 A Based on WO 9806261; EP 926951 A1 Based on WO 9806261; US 6150415 A CIP of US 5955496; US 6174695 B1 Div ex US 5955496

PRAI US 1997-909523 19970812; US 1996-23397P 19960813; US 1999-252148 19990218; US 1999-312207 19990514

IC ICM A01N033-02; A61K031-17; A61K031-34; C12Q001-34

ICS A01N037-02; A01N043-20; A01N043-24; A61K031-13; A61K031-23; A61K031-335; C07D307-12

AB WO 9806261 A UPAB: 20010126

Inflammatory disease is treated by administration of an inhibitor of epoxy hydrolase (EH). Also claimed are: (1) a method for detecting EH inhibition by treating cell cultures having a known level of free intracellular calcium ion with a tetrahydrofuran diol (II; metabolite of arachidonic acid (AA)) or a leucotoxindiol (III; metabolite of a leucotoxin epoxide) and determining the change in Ca ion level; (2) poly- or mono-clonal antibodies (Ab) against (II), and (3) an isolated biologically active (II).

(I) inhibit formation of (II) or dihydroxy lipids and is an antisense molecule; substrate mimic; chalcone oxide (particularly 4-(phenyl or fluoro)chalcone oxide); a phenyl glycidol (especially S,S-4-nitrophenylglycidol); a lipid alkoxide (especially 9-methoxystearic acid) or a lipophilic carbodiimide (especially dicyclohexyl carbodiimide). In the assay of (1), insect cells transfected with a baculovirus expressing EH may be used. Alternatively, to identify agents with reduced side effects in vivo, mammalian cells, especially pulmonary alveolar epithelial cells, are used and calcium influx is monitored.

USE - The method is specified for treatment of adult respiratory distress syndrome (ARDS), but can also be used to treat other diseases mediated by polyunsaturated lipid metabolites, e.g. systemic inflammatory response syndrome. The method (1) is used to identify (I) and Ab are useful for detection and purification of (II), for determining susceptibility to ARDS and for monitoring the progress or treatment of this condition (or of diabetes or other inflammatory diseases). Also (not claimed) leucotoxins, (III), (II) and other oxylipins are useful as (pro)drugs, e.g. as antimicrobials in animals and plants. (III) may also be a selectable marker for recombinant plants or used for control of plant pathogens. The process is based on the discovery that (II) and (III), and not their epoxide precursors as previously thought, are responsible for symptoms of ARDS and increase inflammation. Dosage of (I) is 0.001-100  $\mu$  mole/kg/day, given orally, parenterally or as a suppository.

Dwg.0/2

FS CPI

FA AB; DCN

MC CPI: B10-A24; B14-C03; B14-D07C; D05-H08; D05-H09; D05-H11

=> d his

(FILE 'REGISTRY' ENTERED AT 16:28:38 ON 21 JUN 2002)

DEL HIS

E LINOLEIC ACID/CN

L1 1 S E3

L2 5 S C18H32O2/MF AND 9 12 OCTADECADIENOIC ACID NOT (LABELED OR (D

FILE 'HCAPLUS' ENTERED AT 16:30:25 ON 21 JUN 2002

E LEUKOTOXINDIOL

L3 15 S E1,E4,E5 (L) DIOL

FILE 'REGISTRY' ENTERED AT 16:32:01 ON 21 JUN 2002

L4 1 S 189191-41-1

L5 10 S C18H34O4/MF AND 12 OCTADECENOIC ACID AND 9 10 DIHYDROXY NOT

L6 10 S L4,L5

FILE 'HCAPLUS' ENTERED AT 16:33:44 ON 21 JUN 2002

L7 33 S L6

L8 39 S L3,L7

L9 100 S (L1 OR LINOLEIC ACID) (L)DIOL

L10 125 S L8,L9

L11 8 S L10 AND (?HYPERTENS? OR ARDS OR (ADULT OR ACUTE) (L)RESPIR?(L)  
E HAMMOCK B/AU

L12 510 S E3-E8

E ZUREK G/AU

L13 8 S E3,E4

E GEE S/AU

L14 148 S E3-E10,E21,E22

E NEWMAN J/AU

L15 81 S E3,E29

E NEWMAN JOHN/AU

L16 318 S E3,E36,E37

L17 12 S L10 AND L12-L16

E CARDIOVASCULAR/CT

E E6+ALL

L18 67 S E1

E E2+ALL

L19 5360 S E4

L20 281115 S E3+NT

E HYPERTENSION/CT

E E3+ALL

L21 33653 S E2+NT

E E8+ALL

L22 23168 S E3+NT

L23 40210 S E8+NT

L24 118127 S E7+NT

E ADULT RESPIRATORY DISTRESS SYNDROME/CT

E E3+ALL

L25 31 S E1

L26 1395 S E2

E PREECLAMPSIA/CT

E E3+ALL

L27 2169 S E3,E4,E2+NT

L28 3737 S E3-E9/BI

E LIPID METABOLISM/CT

E E3 ALL

E LIPID METABOLISM/CT

E E3+ALL

L29 11021 S E1,E2

L30 6 S L10 AND L18-L29

L31 14 S L11,L17,L30

E FATTY ACIDS/CT

E FATTY ACIDS(L)D/CT

E UNSATURATED FATTY ACIDS/CT

E E3+ALL

L32 8133 S E1,E2

L33 48 S L32 (L) (DIHYDROXY# OR DIOH OR DIOL OR DI HYDROXY# OR DI OH)

L34 13 S L33 NOT (PLASTIC# OR COATING?)/SC,SX

L35 3 S L34 AND (1 OR 9 OR 63)/SC,SX

L36 320 S L32 AND L18-L29

L37 5 S L36 AND 9/SC

SEL DN 2

L38 1 S L37 AND E1  
 L39 422 S L32 (L) (ANT OR ANST)/RL  
 L40 6 S L39 AND L36  
 SEL DN 3  
 L41 1 S L40 AND E2  
 L42 15 S L31,L38,L41  
 L43 1 S L10 (L) (ANT OR ANST)/RL  
 L44 0 S L10 AND (BLOOD ANALYSIS OR URINALYSIS)  
 L45 8 S L10 AND ?ASSAY?  
 SEL DN 1 2 5  
 L46 3 S L45 AND E3-E5  
 L47 16 S L42,L46  
 L48 0 S L10 AND ELISA  
 L49 7 S L10 AND (BLOOD OR URINE)  
 E BLOOD/CT  
 E E3+ALL  
 L50 4 S L10 AND E2+NT  
 L51 0 S L10 AND (E136+NT OR E139+NT OR E145+NT)  
 E URINE/CT  
 E E3+ALL  
 L52 0 S L10 AND E3+NT  
 L53 1 S L10 AND E2+NT  
 L54 5 S L10 AND E1+NT  
 E URINE ANALYSIS/CT  
 E E3+ALL  
 L55 0 S L10 AND E3,E2+NT  
 L56 24 S L47,L49,L50,L53,L54  
 L57 9 S L56 AND L1,L2  
 L58 16 S L56 AND ?LINOLE?  
 L59 17 S L57,L58  
 L60 7 S L56 NOT L59  
 L61 6 S L60 NOT WASP  
 L62 23 S L59,L61  
 SEL DN 6 18 19 20 21 22 23  
 L63 16 S L62 NOT E1-E7  
 L64 16 S L63 AND L3,L7-L63  
 L65 14 S L64 AND LEUKOTOX?  
 L66 16 S L64,L65  
 L67 7 S LINOLE? (L) ?GLUCURON? (L) ?CONJUGAT?  
 SEL DN 1  
 L68 1 S L67 AND E8  
 L69 16 S L66,L68  
 SEL HIT RN

FILE 'REGISTRY' ENTERED AT 17:05:40 ON 21 JUN 2002

L70 3 S E9-E11

FILE 'REGISTRY' ENTERED AT 17:05:59 ON 21 JUN 2002

FILE 'HCAPLUS' ENTERED AT 17:06:08 ON 21 JUN 2002

FILE 'REGISTRY' ENTERED AT 17:07:30 ON 21 JUN 2002

L71 1 S 73889-55-1

FILE 'HCAPLUS' ENTERED AT 17:07:40 ON 21 JUN 2002

L72 13 S L71  
 L73 5 S L72 AND L12-L16  
 L74 1 S L72 AND L18-L29  
 L75 5 S L73,L74 AND L69  
 L76 8 S L72 NOT L75

FILE 'REGISTRY' ENTERED AT 17:08:58 ON 21 JUN 2002

FILE 'HCAPLUS' ENTERED AT 17:09:11 ON 21 JUN 2002

FILE 'BIOSIS' ENTERED AT 17:09:26 ON 21 JUN 2002

E HAMMOCK B/AU  
L77 510 S E3,E4,E7-E9  
E ZUREK G/AU  
L78 6 S E3,E4  
E GEE S/AU  
L79 112 S E3,E8,E22,E23  
E NEWMAN J/AU  
L80 264 S E3,E29  
E NEWMAN JOHN/AU  
L81 19 S E3  
L82 12 S E15  
L83 3 S E16  
L84 9 S L6,L71  
L85 566 S ?LEUKOTOXIN?  
L86 14 S L85 (L) DIOL  
L87 18 S L84,L86  
L88 16 S L77-L84 AND L87  
L89 2 S L87 NOT L88  
L90 18 S L87-L89  
L91 3 S L90 AND 00520/CC  
L92 3 S L90 AND CONFERENCE/DT  
L93 3 S L91,L92  
L94 15 S L90 NOT L93  
SEL DN 8 13  
L95 2 S E1-E2  
L96 5 S L93,L95 AND L77-L95

FILE 'BIOSIS' ENTERED AT 17:14:13 ON 21 JUN 2002

FILE 'MEDLINE' ENTERED AT 17:14:30 ON 21 JUN 2002

L97 11 S L84,L86

FILE 'WPIX' ENTERED AT 17:15:51 ON 21 JUN 2002

L98 30 S ?LEUKOTOXIN? OR ?LEUKO TOXIN?  
L99 0 S L98 (L) DIOL  
L100 10 S ?LEUCOTOXIN? OR ?LEUCO TOXIN?  
L101 1 S L100 AND DIOL  
L102 36 S LINOLEIC ACID (L) DIOL  
L103 3 S LINOLEIC ACID (L) ?GLUCUR?  
L104 0 S LINOLEIC (L) ?CONJUGAT? (L) ?GLUCU?  
L105 5 S LINOLE? (L) ?GLUCU?  
E HAMMOCK B/AU  
L106 15 S E4  
E ZUREK G/AU  
E GEE S/AU  
L107 12 S E3-E7  
E NEWMAN J/AU  
L108 54 S E3,E25  
L109 2 S L98,L100,L102,L103,L105 AND L106-L108  
L110 2 S L101,L109

FILE 'WPIX' ENTERED AT 17:21:45 ON 21 JUN 2002